

Energy metabolism in neurodevelopment and medulloblastoma

Katherine Tech^{1,2}, Timothy R. Gershon^{2,3,4}

¹Joint Department of Biomedical Engineering, NC State University and UNC Chapel Hill, Chapel Hill, NC 27599, USA; ²Department of Neurology, ³Lineberger Comprehensive Cancer Center, ⁴UNC Neuroscience Center, University of North Carolina School of Medicine, Chapel Hill, NC 27599, USA

Correspondence to: Timothy R. Gershon, MD, PhD. Department of Neurology, CB 7025, UNC School of Medicine, Chapel Hill, NC 27599, USA. Email: gershont@neurology.unc.edu.

Abstract: New, less toxic therapies are needed for medulloblastoma, the most common malignant brain tumor in children. Like many cancers, medulloblastomas demonstrate metabolic patterns that are markedly different from the surrounding non-neoplastic tissue and are highly organized to support tumor growth. Key aspects of medulloblastoma metabolism, including increased lipogenesis and aerobic glycolysis are derived from the metabolic programs of neural progenitors. During neural development, Sonic Hedgehog (Shh) signaling induces lipogenesis and aerobic glycolysis in proliferating progenitors to support rapid growth. Shh-regulated transcription induces specific genes, including hexokinase 2 (*Hk2*) and fatty acid synthase (*FASN*) that mediate these metabolic patterns. Medulloblastomas co-opt these developmentally-regulated patterns of metabolic gene expression for sustained tumor growth. Additionally, medulloblastomas limit protein translation through activation of eukaryotic elongation factor 2 kinase (eEF2K), to restrict energy expenditure. The activation of eEF2K reduces the need to generate ATP, enabling reduced dependence on oxidative phosphorylation and increased metabolism of glucose through aerobic glycolysis. Lipogenesis, aerobic glycolysis and restriction of protein translation operate in a network of metabolic processes that is integrated by adenosine monophosphate-activated protein kinase (AMPK) to maintain homeostasis. The homeostatic effect of AMPK has the potential to limit the impact of metabolically targeted interventions. Through combinatorial targeting of lipogenesis, glycolysis and eEF2K, however, this homeostatic effect may be overcome. We propose that combinatorial targeting of medulloblastoma metabolism may produce the synergies needed for effective anti-cancer therapy.

Keywords: Medulloblastoma; glycolysis; lipogenesis; eukaryotic elongation factor 2 kinase (eEF2K)

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Introduction

Metabolically-targeted therapies hold the promise of offering newly effective, less toxic treatment for medulloblastoma, the most common malignant brain tumor of childhood. Current therapy relies on the sensitivity of medulloblastoma to DNA damage that was discovered more than 50 years ago. Craniospinal radiation therapy, first implemented in the 1950s, changed medulloblastoma from a uniformly fatal disease into a treatable cancer with 60% long-term survival (1). Since then, decades of clinical trials have produced incremental improvement in outcomes by

adding chemotherapy, with 80% of standard risk patients and 70% of high risk patients surviving more than 5 years (2-6). The success of radiation and chemotherapy however, comes at significant costs, as survivors must live with untoward effects of treatment, including dementia, early strokes, growth impairment and hearing loss (7-14). Survivors also remain at risk of recurrence, which is presently incurable, and 20-30% of medulloblastoma patients eventually die of disease (2,15,16). Finding new tumor-specific vulnerabilities to complement sensitivity to DNA damage may allow new approaches to therapy. Recent investigations suggest that the metabolic program of medulloblastoma may be a

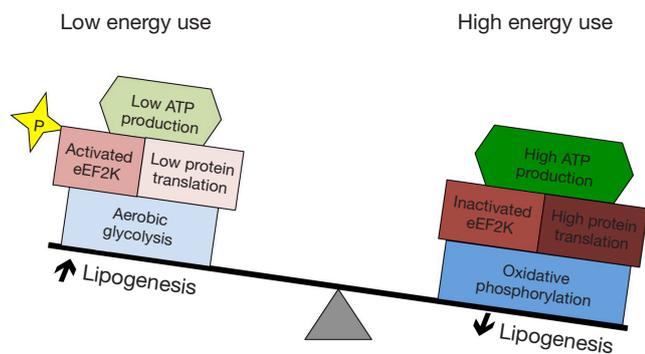


Figure 1 Proliferating cells must balance energy demands with biosynthesis requirements. During rapid growth, cells increase aerobic glycolysis to generate intermediates for biosynthetic pathways, such as lipogenesis, and to maintain low ATP production. Likewise, phosphorylated eEF2K actively reduces global protein translation to conserve energy and redirect cellular energy expenditure towards biomass accumulation. While oxidative phosphorylation efficiently generates ATP, allowing for high protein translation, it does not provide the substrates needed for lipogenesis. eEF2K, eukaryotic elongation factor 2 kinase.

previously untested vulnerability.

Here, we review specific features of medulloblastoma metabolism that may be targeted therapeutically. Some metabolic processes typical of medulloblastoma, including increased lipogenesis and aerobic glycolysis, derive from neural development. Other metabolic processes, including global inhibition of protein translation, may not have a clear developmental correlate but rather may be common features of cancer. We propose that these diverse metabolic processes are interrelated, as shown in *Figures 1,2*, and may be targeted in concert to maximize the potential anti-tumor effect.

Neural progenitors and medulloblastoma cells share distinct metabolic needs

Medulloblastoma is a molecularly heterogeneous set of tumors that arise from the cerebellum, share common histologic patterns, but arise from different sets of neural progenitors. Two molecular subgroups of medulloblastoma have been related to hyperactivation developmental signaling pathways, specifically Sonic Hedgehog (Shh) and WNT. Lineage tracing in transgenic mice demonstrates that activation of these pathways transforms distinct but related sets of neural progenitors. Shh hyperactivation

drives medulloblastoma formation specifically in cerebellar granule neuron progenitors (CGNPs), a population that derives from the upper rhombic lip (17,18). WNT pathway activation, combined with p53 deletion, drives medulloblastoma formation from brain stem progenitors that derive from the lower rhombic lip (19). The mitotic effect of Shh on CGNPs and the oncogenic effect of Shh-pathway hyperstimulation provide an ideal experimental platform to study metabolic patterns as neural progenitors proliferate and give rise to progenitor-derived tumors.

Both neural progenitors and tumor cells face metabolic challenges that distinguish them from other cells in the brain. All cells consume energy as they maintain homeostasis, and all cells in the brain produce energy from glucose, ketones and amino acids. Neurons, which are post-mitotic cells, are the largest energy consumers in the brain, expending energy to maintain electrical activity and intercellular communication (20,21). The efficiency of ATP generation may therefore be of paramount importance. The need for efficient ATP generation in proliferating cells in the brain, however, may be balanced by additional metabolic needs.

Unlike post-mitotic neurons, proliferative cells must not only extract energy from substrates, but also metabolize these substrates into the nucleic acids, proteins and lipids for their progeny (22). In the first 2 post-natal weeks in mice, and in the first year of life in humans, the cerebellum is the site of rapid proliferation, as CGNPs divide in response to Shh signaling. CGNP proliferation generates the largest population of neurons in the brain. For the highly proliferative CGNPs, the generation of intermediates for the synthesis of lipids, nucleic acids and proteins may compete for priority with the downstream generation of ATP. Cells of high-grade tumors, including medulloblastoma and glioblastoma, must similarly balance energy metabolism with the need to synthesize the macromolecules essential for tumor growth. Lower grade tumors, in contrast, may not require constant accumulation of biomass, and can therefore prioritize ATP production. The different metabolic needs of proliferative and non-proliferative cell populations are matched by profound differences in their mechanisms of nutrient metabolism.

Neural progenitor cells configure metabolism to support lipogenesis

In concert with the induction of proliferation, Shh induces lipogenesis in CGNPs through a mechanism that

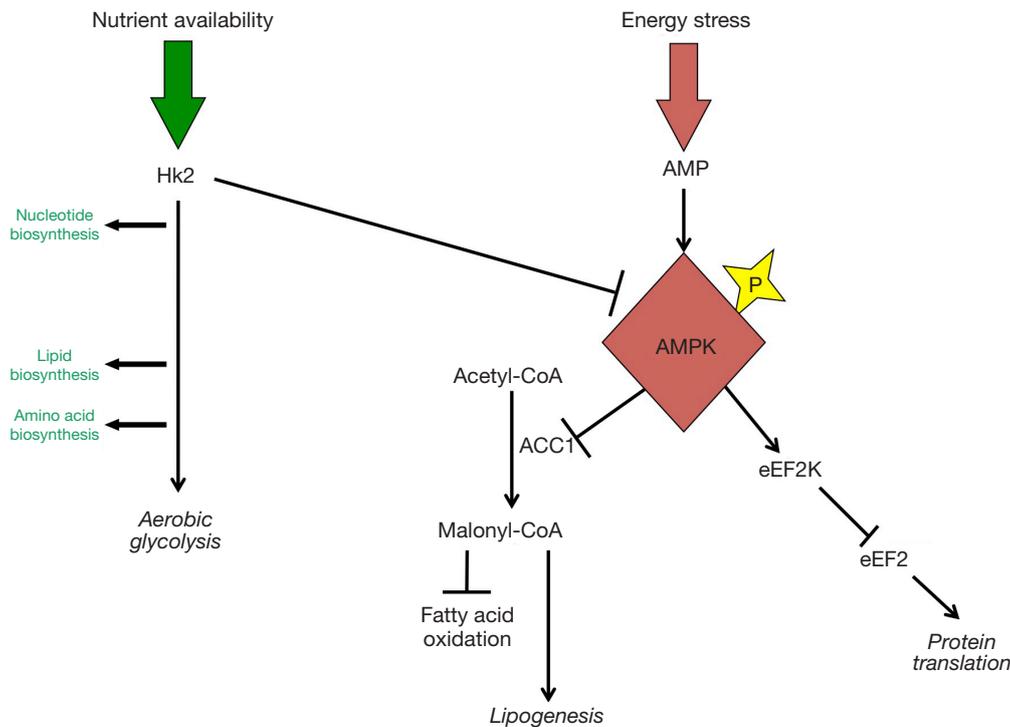


Figure 2 AMPK is a regulatory node in energy metabolism. Proliferating cells use Hk2-dependent aerobic glycolysis when glucose is not scarce, enabling the use of glucose intermediaries for biosynthesis. Hk2 deletion induced AMPK activation in medulloblastoma, suggesting that Hk2 functions in tumors to maintain AMPK in an inactive state. During energy stress, increasing AMP:ATP ratio induces the phosphorylation and activation of AMPK. In turn, activated AMPK phosphorylates eEF2K and ACC1, to decrease protein translation and lipogenesis, respectively, while increasing fatty acid oxidation. AMPK thus maintains energy homeostasis in part by balancing lipogenesis and protein translation. Blocking both lipogenesis and the inhibition of translation may disrupt this homeostatic effect and improve the effectiveness of metabolic therapy. ACC1, acetyl-CoA carboxylase 1; AMP, adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; eEF2, eukaryotic elongation factor 2; eEF2K, eukaryotic elongation factor 2 kinase; Hk2, hexokinase 2.

is preserved in medulloblastoma (23–25). At the level of transcriptional regulation, Shh pathway activation up-regulates proteins required for lipid synthesis, including fatty acid synthase (FASN) and acetyl-CoA carboxylase 1 (ACC1), and down-regulates fatty acid catabolism enzymes, including acyl-CoA oxidase 1 (ACOX1) and medium chain acyl-CoA dehydrogenase (MCAD). These transcriptional changes are mirrored by changes in the metabolic activity of CGNPs, demonstrated *in vitro* where Shh decreases CGNP fatty acid oxidation (24). The transcriptional regulation of lipid metabolism enzymes in CGNPs is coordinated by Shh-dependent activation of E2F1 via Rb modulation (24). Through this system, Shh induces both increased cell cycling and increased lipogenesis, thus ensuring that macromolecule biosynthesis is coupled with proliferation. Likewise, Shh further induces changes in glucose metabolism to support biosynthesis.

Aerobic glycolysis allows neural progenitors to balance energy and biosynthesis requirements

Glucose is the primary energy source in the brain. Through oxidative phosphorylation, glucose may be metabolized to H_2O and CO_2 to generate 38 ATP per molecule. Alternatively, glucose may be metabolized to pyruvate through glycolysis, ultimately generating lactate and 2 ATP. Aerobic glycolysis is the metabolism of glucose to lactate despite the presence of sufficient oxygen needed for oxidative phosphorylation. Cells with large ATP requirements are likely to be disadvantaged by aerobic glycolysis because glycolysis generates less ATP per molecule of glucose than oxidative phosphorylation. Proliferating cells, however, may use aerobic glycolysis to satisfy the competing needs for both energy generation and the accumulation of biomass (Figure 1). Unlike oxidative phosphorylation, which converts

glucose to H₂O and CO₂, aerobic glycolysis also generates metabolic intermediates that can be used for lipid and nucleic acid biosynthesis (26). Consistent with their different energy requirements, neurons and neural progenitors use specific sets of glucose metabolizing enzymes that promote either oxidative phosphorylation or aerobic glycolysis.

Differentiated neurons and neural progenitors metabolize glucose using distinct sets of glycolytic enzymes. Hexokinases catalyze glucose phosphorylation, the first modification of glucose upon entry into the cell. There are four mammalian genes coding for hexokinases (*Hk1-4*). *Hk1* is expressed by neurons and glia throughout the brain but excluded from regions of neural progenitors (27). In contrast, *Shh* signaling induces *Hk2* expression in CGNPs (27). Further downstream in the glycolytic pathway, *Shh* induces splicing of the enzyme pyruvate kinase into the M2 isoform (*PkM2*) (23,28).

In diverse cell types, *Hk2* and *PkM2* are associated with aerobic glycolysis and metabolomic analysis demonstrates that *Shh* induces aerobic glycolysis in CGNPs (23,27). Cerebellar glucose uptake and lactate generation are specifically increased during the period of postnatal cerebellar neurogenesis, and CGNPs cultured in the presence of *Shh* increase glucose uptake and lactate generation, without increasing oxygen consumption (27). Genetic deletion of *Hk2* in CGNPs blocked *Shh*-induced aerobic glycolysis, demonstrating the central role of *Hk2* in configuring CGNP metabolism in response to *Shh* signaling.

The expression of *PkM2* in response to *Shh* suggests that this isozyme also plays an important role in CGNP growth and metabolism. *PkM2* has been widely held to be an oncogene because it is ubiquitously expressed in cancer. A seminal study comparing xenografts engineered to express either *PkM1* or *PkM2* showed the M2 isoform conferred a growth advantage (29). Since then, a variety of oncogenic mechanisms have been attributed to *PkM2*, including metabolic reprogramming, histone phosphorylation and direct regulation of gene expression (30-33). More recently, *PkM2* has been proposed to promote proliferation by acting as a regulated, inefficient converter of phosphoenolpyruvate (PEP) to pyruvate (34). In response to external and internal signals, such as changes in nutrient availability, *PkM2* activity can be modulated to fulfill metabolic demands. Down-regulating the catalytic activity of *PkM2* slows the flow of PEP through glycolysis, increases the supply of intermediates upstream of PEP, and allows for alternative uses of PEP, including the activating phosphorylation of the enzyme phosphoglycerate mutase 1 (*Pgam1*) (35). *Pgam1* in turn may promote the shunting of intermediates into

anabolic pathways through its effects on the balance of 2- and 3-phosphoglycerate, which feedback on serine synthesis and the pentose phosphate pathway (36). Through these mechanisms, *PkM2* may increase the efficiency with which aerobic glycolysis fulfills the biosynthetic needs of CGNPs.

Increased lipogenesis and aerobic glycolysis in medulloblastoma

Malignant brain tumor cells, like neural progenitors, are highly proliferative and must meet the competing needs to generate energy through nutrient catabolism and to convert nutrients into macromolecules necessary for growth. The transcriptional regulators and enzymes that mediate increased lipogenesis and aerobic glycolysis in *Shh*-stimulated CGNPs also control the metabolism of tumor cells in mouse models of *Shh*-driven medulloblastoma. The ND2:*SmoA1* and *SmoM2* mouse lines, express different, constitutively active alleles of the *Shh* effector *Smoothed* and develop spontaneous medulloblastomas. These tumors demonstrate up-regulation of *FASN*, *E2F1* activation and deposition of lipid droplets, indicating a high rate of lipid synthesis (24), and up-regulation of *Hk2* and *PkM2*, consistent with increased aerobic glycolysis (23,27). The glycolytic metabolism of medulloblastoma is further demonstrated by ¹⁸FDG PET studies that show intense glucose avidity of medulloblastomas in both mice and humans, even when compared to the typically high glucose uptake of the brain (27,37).

Aerobic glycolysis and lipogenesis as common features across brain tumor types

While the aerobic glycolysis and lipogenesis have been most extensively studied in *Shh*-driven medulloblastoma, these metabolic patterns may be common across medulloblastoma subgroups. Whether FDG avidity in the human disease varies with subtype is not known. *WNT* pathway activation has been shown to increase glycolysis at the expense of oxidative phosphorylation in both normal and transformed cells outside the brain (38,39). The *MYC* family of transcription factors is known to up-regulate glycolysis in diverse cancers (40-42) and several lines of evidence suggest that *MYC* activation may be a key point of convergence that shapes medulloblastoma metabolism across subgroups. *MycN* operates downstream of *Shh* to drive aerobic glycolysis in CGNPs and *Shh*-driven medulloblastoma in *SmoM2* mice. *WNT* signaling may also promote glycolysis

in part through MYC (43); whether this relationship operates in WNT-subgroup medulloblastomas remains to be tested. Group 3 medulloblastomas are associated with MYC-family amplifications and MycN overexpression in mice produces medulloblastomas that resemble group 3 tumors in gene expression pattern (44,45). While glucose metabolism has not yet been examined in group 3 medulloblastoma or in MycN-driven medulloblastoma in mice, it is likely that in these tumors, as in other cancers, MYC reconfigures metabolism to favor glycolysis. Importantly, aerobic glycolysis plays a key role in malignant brain tumors with diverse pathologies, as glioblastomas like medulloblastomas express Hk2 (46) and demonstrate high glucose uptake in ¹⁸FDG PET studies (47,48). In the activation of lipogenesis and aerobic glycolysis, diverse malignant brain tumors recapitulate the metabolic adaptations of neural progenitors.

Disruption of lipogenesis or glycolysis restricts brain tumor growth

Experimental evidence shows that E2F1-mediated lipogenesis and Hk2-dependent glycolysis play important roles in supporting medulloblastoma progression. In SmoA1 mice, treatment with either the CDK inhibitor olomoucine or the FASN inhibitor C75 significantly inhibited tumor growth and extended animal survival (24). Similarly, genetic deletion of Hk2 in medulloblastoma-prone GFAP-cre:SmoM2 mice significantly inhibited tumor growth. GFAP-cre:SmoM2 mice are a highly penetrant, rapidly progressive, primary medulloblastoma model ideally suited for genetic studies. These mice express a constitutively active allele of the Shh receptor component smoothed throughout the brain and die from medulloblastoma with 100% frequency by postnatal day 20 (18). Genetic deletion of Hk2 in GFAP-cre:SmoM2 mice markedly reduced the aggressiveness of the resulting medulloblastomas, causing tumors to grow as indolent lesions and allowing long-term survival of tumor-bearing mice (27). Importantly, Hk2 deletion was associated in tumors with activation of the intracellular energy regulator protein adenosine monophosphate-activated protein kinase (AMPK), which inhibits ACC1; this feedback through AMPK may operate alongside the generation of metabolites to link aerobic glycolysis to lipogenesis. In glioblastoma xenografts, Hk2 depletion similarly limited tumor growth and increased treatment sensitivity, while Hk2 overexpression enhanced tumor

progression (46). Taken together, these results suggest that inhibiting the metabolic adaptations common to neural progenitors and brain tumors may be a novel approach to brain tumor therapy. The integration of glycolysis and lipogenesis in progenitors suggests that targeting both processes in combination may reinforce the anti-tumor effect.

Restriction of energy expenditure in medulloblastoma enables tumor metabolism

Mechanisms that limit energy consumption enable tumors to maximize lipogenesis and to benefit optimally from aerobic glycolysis. While metabolizing glucose through glycolysis supports the channeling of nutrients into biosynthesis, the inefficient production of ATP presents a risk if nutrient availability is compromised. Minimizing tumor energy consumption may mitigate this risk. The net conversion of glucose to lipid is also a liability unless energy needs can be lessened. A mechanism for limiting tumor energy expenditure by inhibiting mRNA translation has recently been described and found to be active in medulloblastoma (49). This mechanism may be essential in allowing tumor cells to fully engage in the lipogenic and glycolytic mechanisms of neural progenitors without the liability of energy scarcity (*Figure 1*).

The eukaryotic elongation factor eukaryotic elongation factor 2 (eEF2) plays an essential role in translation by promoting GTP-dependent translocation of the growing peptide chain along the ribosome (50). The activity of eEF2 is down-regulated through phosphorylation by eukaryotic elongation factor 2 kinase (eEF2K) (51). In turn, eEF2K is activated by the energy sensor AMPK (52,53). Expression of eEF2K correlates negatively with patient survival in both medulloblastoma and glioblastoma, suggesting that reducing eEF2 activity promotes tumor growth (49). Consistent with this interpretation, disruption of eEF2K expression in xenografted cell lines sensitized tumors to nutrient deprivation, causing tumors in mice fed calorie-restricted diets to grow more slowly and with increased tumor cell death (49).

Combinatorial targeting of tumor metabolism

Reducing energy expenditure through eEF2K-mediated translation inhibition enables tumor cells to increase aerobic glycolysis, which in turn supports lipogenesis. Simultaneously targeting each of these processes may

maximize stress to the tumor cell. While individually disrupting Hk2 or FASN slowed tumor growth, neither intervention matched the strong response induced by radiation. Specific inhibitors of Hk2, FASN and eEF2K may produce synergistic effects, however, and should be tested experimentally in combination in order to maximize potential effect. Similarly, a ketogenic diet may effectively target both lipogenesis and glycolysis by reducing nutrient availability for these pathways. A high-fat, low carbohydrate diet shifts the primary energy substrate for energy metabolism away from glucose to ketone bodies generated from fatty acid catabolism. Normal brain metabolism inherently relies on ketone bodies as an alternative energy source, thus a shift away from glucose metabolism may induce energy stress on the glucose-dependent tumor while minimally affecting energy balance in the normal brain (54). While the implementation of a ketogenic diet as a therapy for medulloblastoma has not been described, case reports describe modest benefits for patients with glioblastoma (55-58). A more robust effect may result from combination with eEF2K inhibition.

Intriguingly, the intracellular energy sensor protein AMPK represents a point of convergence between these different processes (Figure 2). AMPK exerts a homeostatic effect by integrating lipogenesis, energy production and protein translation. Targeting AMPK may be problematic however, as activation and inhibition of AMPK have the potential for mixed effects on growth. AMPK activation inhibits lipogenesis through inhibitory phosphorylation of ACC1 (59-61), which may restrict tumor growth. Consistent with a tumor suppressive effect, Hk2 deletion produced AMPK activation in GFAP-cre:SmO₂ medulloblastomas while slowing tumor growth (27). AMPK activation, however, also phosphorylates eEF2K, which may promote growth by limiting energy expenditure (51,62). In order to disrupt the homeostatic effect of AMPK-mediated integration, it may be most effective to directly target simultaneously lipogenesis, eEF2K and aerobic glycolysis. A ketogenic diet combined with specific inhibitors of Hk2 and/or eEF2K may achieve this goal and optimally target tumor metabolism.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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