REVIEW

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Brain cancer metabolism

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Summary

Malignant brain tumors represent a serious health issue concerning both children and adults, and are often difficult to manage. Tumor metabolism has recently emerged as a promising target for new cancer treatment. Malignant brain tumors strongly depend on glycolysis for energy, predominantly using glucose and glutamine, whereas healthy brain cells primarily utilize ketone bodies under reduced glucose supply. As a metabolic disorder involving the dysregulation of glycolysis and cellular respiration, there is hope that brain cancer could be at least partially managed through changes in the metabolic environment. The objective of this review is to examine the metabolic changes in brain tumors and to summarize the latest knowledge of certain metabolic processes in tumorigenesis, as well as the associated potential therapeutic approaches.

KEYWORDS: *brain tumors; cancer metabolism; metabolic pathways; metabolic therapy*

BACKGROUND

Primary brain tumors represent about 2% of all primary tumors in adults and 23% of all childhood cancer diagnoses, with increasing incidence in both populations. Primary malignant brain cancer causes substantial morbidity and mortality in adults and is the second leading cause of cancer death in children(1). The cure rate for malignant types of these lesions is significantly lower than for most other types of cancer. Current standard therapies generally involve maximal surgical resection followed by chemotherapy with or without radiation therapy(2).

Despite considerable investments in research and further development of treatment options, the survival rates and quality of life for these patients have not significantly improved(3). However, the scientific community has recently made notable breakthroughs in studies concerning the metabolic nature of malignant disease. As brain tumor metabolism is being better understood each day, new therapeutic approaches to brain cancer management are being recognized.

Most cancer, including brain cancer, is primarily a disease of energy metabolism. In contrast to normal brain tissue, which can oxidize either glucose or ketone bodies for energy, malignant brain tumors use glucose and glutamine as major metabolic fuels, as they lack metabolic flexibility

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for the use of ketone bodies. As a metabolic disorder involving the dysregulation of glycolysis and cellular respiration, brain cancer could theoretically be managed through changes in the metabolic environment, in addition to current treatment protocols. An understanding of how main metabolic pathways are modified by cancer cells, and the interactions between oncogenes and tumor suppressor genes with these pathways, may enlighten new strategies in the treatment of primary malignant brain tumors.

ENERGY METABOLISM IN HEALTHY BRAIN CELLS

Under physiological conditions, the brain derives almost all of its energy from the aerobic oxidation of glucose(4). The glucose transporter enriched in the brain capillary endothelial cells, GLUT-1, facilitates the diffusion of glucose through the blood-brain barrier. Most of the glucose is metabolized to pyruvate, which enters the mitochondria of neurons and glia and is converted to acetyl-CoA before entering the tricarboxylic acid (TCA) cycle. Under normal conditions, only about 13% of glycolytic pyruvate is converted to lactate(5). Due to limited uptake from the circulation, free fatty acids are not considerably metabolized by brain cells for energy.

While glucose is the preferred energy substrate of normal neurons and glia, these cells will metabolize ketone bodies for energy under fasting-induced decreased blood glucose levels. Since the concentration of ketones in the blood is inversely proportional to that of glucose, the brain does not normally metabolize ketone bodies for energy unless blood glucose levels are reduced(6). Brain ketone body metabolism is a conserved physiological adaptation to prolonged food restriction that has evolved to enable survival and maintain adequate brain function while sparing proteins(7).

Ketone bodies, consisting of acetoacetate, β-hydroxybutyrate, and acetone, are derived from fat catabolism in the liver and are transported into the brain through the monocarboxylic transporters on the blood-brain barrier. In contrast to glucose, ketone bodies bypass cytoplasmic glycolysis and directly enter the mitochondria, where they are promptly oxidized to acetyl-CoA. The amount of acetyl-CoA formed from ketone body metabolism is more significant than that formed from glucose metabolism. Given that ketone bodies are more energy efficient than pyruvate or fatty acids and that the increase of ATP induced by ketone bodies is also achieved using less oxygen, ketone bodies are considered to be a *super fuel*(8).

Even so, the brain still favors the utilization of glucose over ketone bodies in physiological conditions due to its high energy demand and the limitations in ketone metabolism under normal circumstances. While ketone bodies can partially support brain energy needs during glucose scarcity, high blood levels are required for the brain to use them efficiently, which typically happens only in prolonged fasting or ketogenic states. Consequently, glucose remains the primary fuel for optimal brain function, especially for maintaining synaptic activity and cognitive processes(9).

ENERGY METABOLISM IN BRAIN TUMORS

In contrast to normal neurons and glia, which readily transition to ketone bodies for energy under conditions of reduced glucose, malignant brain tumors are strongly dependent on glycolysis for energy. Only healthy cells with a flexible genome and normal mitochondria can effectively transition from one energy state to another. In tumor tissue, developed mutations restrict genomic and metabolic flexibility, thus making tumor cells more vulnerable to energy stress. Cancer cells adapt to their environment by reprogramming their cellular metabolism, which allows them to grow, survive, and proliferate at an increased rate, which is a major characteristic of these cells. The resulting metabolic rewiring in cancer cells is not a passive process but a direct work of oncogenes and inactivated tumor suppressors(10). Predominant nutrients that cancer cells use for anabolic processes are glucose and glutamine. Reprogramming of uptake and metabolism of those nutrients seems to be the basis of altered cancer-cell metabolism(11). Targeting these pathways, such as glucose, lipid, or amino acid metabolism, offers a promising strategy to inhibit tumor growth(12).

Alterations in glucose metabolism

The alterations in glucose metabolism in malignant cells have been thoroughly studied for

over a century, beginning with Otto H. Warburg's conclusion that cancer cells tend to metabolize glucose into lactate, even in the presence of adequate oxygen supplies(13). Warburg theorized that the effect of *aerobic glycolysis* was caused by mitochondrial respiratory injury(14) and began to consider it a ubiquitous and central metabolic change in the malignant transformation of cells(15). This theory served as a basis for understanding glucose metabolism in cancer cells.

However, recent studies have shown that the mitochondrial function in tumor cells is not damaged or lost. Instead, mitochondrial metabolism remains functional and able to carry out oxidative phosphorylation, but it is reprogrammed to prioritize macromolecular synthesis(16) needed for tumor progression. Although mitochondrial ATP production is reduced, the high rate of glycolysis compensates by providing both energy and the precursors needed for macromolecular synthesis.

The end product of glycolysis is pyruvate, which is converted to lactate by lactate-dehydrogenase (LDH). LDH is a tetrameric enzyme with two variants, LDHA and LDHB, encoded by separate genes. Malignant cells tend to upregulate lactate dehydrogenase A (LDHA) while downregulating LDHB, which promotes a metabolic switch to aerobic glycolysis, rendering the overexpressed protein a tumor marker and a target for therapy(17). The human body contains five different LDH isozymes, including LDH5, which consists of LDHA subunits. Glioblastoma (GBM) cells, for example, overproduce and secrete excessive amounts of LDH5, which causes healthy myeloid cells to display Natural killer group 2, member D (NKG2D) ligands on their surface. This leads to the down-modulation of the activating NKG2D receptor on natural killer cells, preventing them from recognizing NKG2D ligand-bearing tumors and impairing their ability to attack and eliminate tumors(18).

The mentioned pyruvate residue, converted to lactate, is secreted from the cell. This results in acidification of the microenvironment and, via matrix metalloproteinases, leads to the degradation of the extracellular matrix – facilitating invasion of tumor cells(11). Besides, inhibiting lactate efflux has been shown to decrease glioma invasion in xenograft animal models(19).

The shift in ATP production from the mitochondria to the cytosol supports macromolecular synthesis and limits the production of reactive oxygen species (ROS), typically generated in the mitochondria during oxidative phosphorylation. Thus, tumor cells reduce ROS production and shield themselves from oxidative stress by downregulating mitochondrial activities, including the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS)(20). Additionally, the TCA cycle cannot function as a complete cycle due to the significant flux of intermediates out of the route.

Changes in metabolism often accompany changes in the genome. Metabolic switch is usually associated with the loss of function of the tumor suppressor p53 and uncontrolled activity of the oncogenic protein NFκB(21). Additionally, hypoxia-induced factor 1 (HIF-1) plays a crucial role in this process, especially in GBM, by activating the transcription of multiple genes involved in angiogenesis, cell invasion, autophagy, and metabolic regulation(22).

The pathways, such as the PI3K/AKT cascade, are also important in the metabolic regulation of the tumor, especially in glucose. It stimulates GLUT1 expression, thus facilitating the influx of glucose through HK2, and stimulates PFK1 activity, which promotes aerobic glycolysis. This pathway also makes the tumor cells very sensitive to high levels of glucose flux. Disrupting the PI3K/AKT pathway leads to reduced glucose consumption, while clinical tests with ^{18}F-deoxyglucose PET imaging showed that the tumor size decreases.

Recent evidence also suggests that certain tumors, such as human and mouse malignant glioma cells, exhibit heterogeneity in glucose metabolism. Specifically, some regions within the same tumor may rely on oxidative phosphorylation for energy production, while others depend primarily on glycolysis(23). This regional metabolic reprogramming is driven by lactic acid, allowing both metabolic phenotypes to coexist: glycolysis predominates in the tumor's interior, while OXPHOS is more active in the lateral regions(24).

Alterations in lipid metabolism

Fatty acids (FA) are essential for both energy production and the synthesis of cellular membranes and are, thus, crucial for cell survival and tumor growth. Due to the high metabolic demand during intense cell proliferation and the development of abnormal blood vessels, tumor tissues are

frequently exposed to hypoxia. FA oxidation requires a large amount of oxygen, and under hypoxic conditions, this process generates reactive oxygen species (ROS), further lowering the limited oxygen supply. The resulting oxidative stress damages membrane lipids and deactivates proteins and enzymes, ultimately leading to apoptotic cell death. To cope with the limited oxygen availability, cancer cells often suppress FA oxidation by reducing intracellular lipolysis, while simultaneously increasing the accumulation of triglyceride lipid droplets (LDs). LDs are cytoplasmic organelles rich in lipids, encased by a single phospholipid layer that surrounds a hydrophobic core of neutral lipids, such as triacylglycerol (TAG) and cholesteryl esters (CEs), alongside a diverse content of proteins(25). These LDs fuel future tumor growth and protect the cells from oxidative stress and lipotoxicity in hypoxia.

A significant storage of LDs has been observed in various tumors, including glioblastoma, where they play a critical role in cancer cell proliferation, resistance to death, and aggressiveness, by regulating energy metabolism and cell signaling. The final step for TAG synthesis is regulated by two diacylglycerol-acyltransferases, DGAT1 and DGAT2. In GBM, DGAT1 is upregulated, facilitating the storage of excess FAs into lipid droplets, providing the cells with an energy reserve. Targeting of DGAT1 in xenograft models blocks lipid droplet formation, induces tumor cell apoptosis, and significantly suppresses GBM growth(26).

The shift in lipid metabolism is mediated by changes in lipid-related gene expression. Among these is sterol regulatory element-binding protein 1 (SREBP1)(27), one of the main transcriptional factors that control lipid metabolism. SREBP1 is upregulated in certain tumors, such as glioblastoma, in response to oncogenic signaling through the EGFR/PI3K/Akt pathway. This leads to enhanced lipid synthesis and uptake, resulting in a higher accumulation of fatty acids than surrounding normal brain tissue(28).

Recent studies suggest that lipid levels reflect the cellular state of the tumor. Targeted lipidomic analysis of multiple patient-derived models revealed a significant shift in lipid metabolism between GBM cancer stem cells (CSCs) and non-CSCs. CSCs are highly plastic tumor cells disseminated throughout the tumor mass, responsive to their environment. They hold self-renewal and tumor initiation capacity responsible for cellular and metabolic heterogeneity, which presents a key challenge to GBM treatment.

GBM CSCs exhibit reduced levels of major classes of neutral lipids compared to non-CSCs. However, they showed a significant increase in the production of polyunsaturated fatty acids by heightened expression of fatty acid desaturase (FADS1/2). This increase is essential for maintaining CSC viability and self-renewal, highlighting the metabolic flexibility of these aggressive cells(29).

Alterations in amino acid metabolism

Dysregulated amino acid metabolism is considered to be an emerging hallmark of cancer. Tumor cells take up amino acids from the extracellular environment as a carbon and nitrogen source for protein and nucleotide synthesis. Controlled oxidation of glutamine carbon skeletons allows the cell to capture its reducing power either in the form of NADH or FADH2, which mediate the transfer of electrons to the electron transport chain, fueling ATP generation. Cofactor NADPH also provides reducing power for a variety of biosynthetic reactions and helps maintain cellular redox capacity. Therefore, an abundant supply of amino acids is important for cancer to sustain its proliferative drive(30).

Glutamine, the most copious amino acid in the plasma, contributes both to the substrate needs of a dividing cell and the control of redox potentials through the synthesis of NADH. In comparison to other amino acids, the importance of glutamine for cell division is significantly higher. After glutamine is taken into the cell, a mitochondrial-associated enzyme, glutaminase-1 (GLS1), converts it to glutamate. Glutamate is then converted to α-ketoglutarate, which enters the TCA cycle in the mitochondria. It can also be converted to aspartate, which contributes to nucleotide synthesis. Excessive amounts of glutamine used by the cell result in alanine and ammonium secretions(31).

Following the success of the ^{18}F-fluorodeoxyglucose (^{18}F-FDG) imaging paradigm, ^{18}F-labeled glutamine tracers have shown promise in preclinical and early clinical studies. Use of ^{18}F-labeled glutamine as a tracer appears to provide useful tumor information where the use of ^{18}F-FDG is not practicable, like in imaging of tumors that are lo-

calized in sites of heavy glucose utilization, such as the brain. As a result, experimental glioma models show selective uptake of ^{18}F-glutamine, compared with surrounding brain tissue(32).

Other than increased glutamine consumption, tumors preferentially uptake the branched-chain amino acids (BCAAs): leucine, isoleucine, and valine, which participate in crucial biochemical functions in the brain and other tissues. The reprogramming of BCAA metabolism alters the levels of important metabolites, including BCAAs, α-ketoglutarate, glutamate, and ROS, ultimately leading to cancer cell survival and rapid expansion. The key proteins in the BCAA metabolic pathway could serve as prognostic and diagnostic biomarkers in cancer, and the metabolic enzymes engaged in BCAA metabolism could be potential therapeutic targets. The significance of BCAA metabolic reprogramming has recently been highlighted in many types of cancer, including glioblastoma. GBM cells excrete large amounts of branched-chain ketoacids (BCKAs), metabolites of BCAA catabolism, through the monocarboxylate transporter 1 (MCT1). BCKAs are taken up by tumor-associated macrophages, predominant cells of the glioblastoma stroma, where they alter their metabolism and phagocytic capacity, possibly enhancing immune suppression in glioblastoma. Targeting the export of BCKAs by inhibiting MCT1 has been shown to impair tumor growth(33).

Macropinocytosis, an opportunistic pathway of amino acid uptake(34), demonstrates the dependency of cancer cell proliferation on amino acid availability. This clathrin-independent endocytosis of extracellular fluid contributes to cancer aggressiveness through nutrient delivery, plasma membrane and receptor recycling, and exosome internalization. Certain macropinocytosis-related genes are overexpressed or down-regulated in glioblastoma patient samples and may represent distinguishing features of GBM in non-tumoral samples and lower-grade gliomas. Thus, macropinocytosis may play an important role in GBM aggressiveness and, therefore, could be targeted for therapy purposes. Macropinocytosis inducers in combination approaches might increase drug uptake in addition to their synergistic effects(35).

Besides macropinocytosis, tumor cells regulate amino acid uptake by modulating the activity of specific amino acid transporters. The expression of neutral amino acid transporter (ASCT2) is up-regulated in many cancer types, including neuroblastoma(36) and glioblastoma(37). Expression of the transporter appears to be under the control of the Myc oncogenes, c-Myc in glioblastoma(37) and n-Myc in neuroblastoma(36,38). In addition, a small competitive molecule antagonist of transmembrane glutamine flux, V-9302, selectively and potently targets the amino acid transporter ASCT2. This leads to the decreased proliferation of tumor cells, raised oxidative stress(40), and increased cell death(39).

Additionally, genes involved in the metabolism of certain amino acids play a critical role in tumor progression. High glutamine metabolism in cancer cells, initiated by its degradation by glutaminases (GA), involves altered expression and/or activity of GA isoforms. In malignant glia-derived tumors, GA isoforms coded by the GLS gene are overexpressed, whereas the GLS2-coded isoforms are hardly detectable. Both the negative modulation of GA isoforms arising from the GLS gene and the introduction of the GLS2 gene product could be successful in decreasing the proliferation and viability of glioblastoma cells(40). Indeed, inhibition of glutaminase with siRNA or small molecule inhibitor has shown reduced growth of glioma cells with mutant IDH1(41).

METABOLIC-RELATED THERAPY OF BRAIN TUMORS

Unfortunately, available standards of care for brain cancer patients are not always successful and remain an important target of continuous research. Limitations and side effects of current types of treatment are being studied, with attention paid to the hope for new approaches. For example, many brain tumor patients receive perioperative corticosteroids as part of the anti-edematous therapy, which can cause elevated blood glucose levels(42). Approximately 30% of patients prescribed glucocorticoids experience elevated blood glucose levels, with around 18% developing steroid-induced diabetes mellitus (SIDM)(43). Since glucose is a major fuel for most glycolysis-dependent brain tumor cells, elevated glucose seems to be associated with poor prognosis, with that connection not being fully understood yet. Also, radiation therapy, while a valuable treat-

ment option for brain cancer, may contribute to oxidative tissue stress, which could theoretically lead to elevated glutamine levels in the tumor microenvironment, potentially supporting tumor activity in some contexts(44). Hence, new approaches are needed that can provide long-term management of malignant brain tumors.

Given the established abnormal energy metabolism in brain tumors, targeting tumor cell energy metabolism becomes an appealing addition to the current standard treatment of patients with brain tumors. The principles of metabolic control theory could theoretically be effective for brain cancer management. Given the differences in energy metabolism between normal brain cells and neoplastic tumor cells, it is apparent that brain tumors will survive in an environment suitable for their energy needs, but once this is restricted or abruptly changed, there is hope that they will grow slower or stop growing.

This general concept is associated with new therapeutic strategies that target tumor cell energy metabolism by lowering circulating blood glucose and elevating ketone bodies, thus targeting brain tumors while enhancing the metabolic efficiency of normal neurons and glia.

Diet interventions

The ketogenic diet (KD) is a high-fat, low-carbohydrate diet that was initially designed as an antiepileptic therapy and, as such, has been used for decades(45). In 1995, the first nutritional metabolic therapy for malignant brain cancer was attempted and has shown the contribution of the KD to long-term tumor management(46). The aim was to shift the main substrate for energy metabolism from glucose to ketone bodies in order to disrupt tumor metabolism while maintaining the nutritional status of patients. More recent cases show that the ketogenic diet is well tolerated and can be an effective non-toxic therapy for malignant brain cancer in both children and adults(47,48). Moreover, the KD could eliminate or reduce the need for adjuvant anticonvulsant and steroidal medications for brain tumor patients as the KD has antiepileptic effects, and when restricted in caloric intake, will naturally elevate circulating glucocorticoid levels(49). Moreover, studies have shown that KD can enhance the effectiveness of standard treatments like chemotherapy and radiation by sensitizing cancer cells to these therapies while protecting normal cells(50). These findings suggest that KD could be an effective multifactorial diet therapy for malignant brain cancer and should be considered as an alternative and complementary therapeutic option.

As with the KD, dietary restriction (DR) reduces glucose and elevates ketone levels, thus inhibiting brain tumor growth. This form of dietary restriction results from a reduced total calorie energy intake without causing a deficiency of any specific nutrient. Previous studies have shown that the anti-tumor effects of DR result more from calorie restriction *per se* than from the restriction of any specific dietary component, such as carbohydrates(51). Caloric restriction improves mitochondrial respiratory function and glutathione redox state in normal cells. Also, ketone bodies protect normal neurons and glia from damage associated with aggressive tumor growth through a variety of neuroprotective mechanisms, including elevated glutathione levels. Thus, DR naturally inhibits glycolysis and tumor growth by lowering circulating glucose levels while at the same time enhancing the vitality of normal cells and tissues through ketone body metabolism(52). Dietary restriction was shown to be anti-angiogenic and pro-apoptotic, as well as anti-invasive(53). Therefore, prescribed diet therapies may represent an effective alternative option in brain cancer therapy.

Concerns regarding the use of metabolic therapy

Despite the need for new treatment options, metabolic therapy is still not sufficiently recognized and implemented in the management of brain tumors due to its non-conventional and non-pharmacological nature. The problem seems to be in recognizing the existence and scientific basis of these alternative metabolic approaches. Hence, physicians should inform patients of these alternative options, especially in a situation when all other treatment modalities have been exhausted.

Another concern is recommending therapy that reduces food intake to patients who may be losing body weight due to cancer cachexia. However, by targeting glycolytically active tumor cells that produce pro-cachexia molecules, dietary restriction therapies can potentially reduce tumor cachexia(54). After the tumor is managed, patients can increase their caloric intake, which will expe-

dite weight gain. Since most neuro-oncologists are still unfamiliar with the application of metabolic therapy for brain cancer management, the lack of a standardized use protocol for all patients presents as a concern. However, several established guidelines have been published; thus, clinicians could begin to adapt these protocols for their brain cancer patients(53).

However, the issue of patient compliance is one of the main reasons why metabolic therapy is not sufficiently explored or generally accepted. Such metabolic and nutritional interventions could pose great difficulties for patients. This type of strict diet regulation, which implies a lifestyle change for most, could be very hard to bear, especially while being aware of your limited life expectancy. This is also the reason why it would be exceptionally demanding to conduct appreciable long-term research regarding this matter. To oversee everything that a whole group of patients consumes over a prolonged period of time would be overly challenging to execute in actuality.

Ultimately, treatment strategies of metabolic therapy have considerable theoretical potential in managing patients with brain cancer. Although clinical evidence is still emerging, metabolic therapy has been associated with improved outcomes in some cases(50,55,56). Ongoing clinical studies also point to the ketogenic diet as a potentially valuable supportive approach, with early results suggesting improvements in metabolic balance and patient quality of life(57–59). However, considering the difficulties of distinctly demonstrating the usefulness of these methods, further intensive research is needed, as well as promoting awareness about this possible, novel treatment option.

CONCLUSION

Brain tumors pose a significant challenge in cancer management due to their aggressive nature, poor prognosis, and lack of therapeutic advances. Despite extensive research, most of the available therapies are only modestly effective in improving the long-term prognosis of people with brain tumors, with significant challenges regarding their toxicity and side-effects.

Recognizing brain cancer as primarily a metabolic disease introduces new revelations and potential therapeutic strategies. Malignant brain tumors strongly depend on glycolysis, for which they predominantly use glucose and glutamine, as opposed to healthy brain cells, which primarily utilize ketone bodies. The reprogramming of main metabolic pathways in cancer cells becomes an appealing target for conducting new therapeutic strategies.

Antitumor therapy typically aims to restrict glucose availability, inhibit key enzymes, and modulate lipid and amino acid metabolism. Following the principles of metabolic control theory, different forms of diet interventions present as non-toxic, therapeutic options that target the energy metabolism of tumor cells by shifting the primary energy source from glucose to ketone bodies, therefore targeting brain tumors while enhancing the metabolic efficiency of healthy brain cells.

Listing potential therapeutic targets related to the metabolic processes of brain tumor cells may enlighten new points of view on fighting brain cancer and improving its outcome, as well as offering hope to a disease that has remained essentially unconquered throughout the ages.

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Sažetak

Metabolizam karcinoma mozga

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Maligni tumori mozga predstavljaju ozbiljan zdravstveni problem, kako kod djece, tako i kod odraslih, te su često neizlječivi. Metabolizam tumora nedavno se istaknuo kao obećavajuća meta za otkrivanje novih mogućnosti u liječenju raka. Maligni tumori mozga snažno ovise o glikolizi za dobivanje energije, za koju pretežno koriste glukozu i glutamin, za razliku od zdravih moždanih stanica koje prvenstveno koriste ketonska tijela u uvjetima smanjene opskrbe glukozom. Kao metabolički poremećaj koji uključuje deregulaciju glikolize i staničnog disanja, postoji nada da bi se tumor mozga mogao barem dijelom kontrolirati promjenama u metaboličkom okruženju. Cilj ovog osvrta jest ispitati metaboličke promjene u tumorima mozga i sažeti najnovija saznanja o određenim metaboličkim procesima tumorigeneze, kao i potencijalne terapijske pristupe povezane s njima.

KLJUČNE RIJEČI: *tumori mozga; metabolizam raka; metabolički putevi; metabolička terapija*