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Review

Metabolic management of brain cancer ☆

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ABSTRACT

Malignant brain tumors are a significant health problem in children and adults. Conventional therapeutic approaches have been largely unsuccessful in providing long-term management. As primarily a metabolic disease, malignant brain cancer can be managed through changes in metabolic environment. In contrast to normal neurons and glia, which readily transition to ketone bodies (β-hydroxybutyrate) for energy under reduced glucose, malignant brain tumors are strongly dependent on glycolysis for energy. The transition from glucose to ketone bodies as a major energy source is an evolutionary conserved adaptation to food deprivation that permits the survival of normal cells during extreme shifts in nutritional environment. Only those cells with a flexible genome and normal mitochondria can effectively transition from one energy state to another. Mutations restrict genomic and metabolic flexibility thus making tumor cells more vulnerable to energy stress than normal cells. We propose an alternative approach to brain cancer management that exploits the metabolic flexibility of normal cells at the expense of the genetically defective and metabolically challenged tumor cells. This approach to brain cancer management is supported from recent studies in mice and humans treated with calorie restriction and the ketogenic diet. Issues of implementation and use protocols are presented for the metabolic management of brain cancer. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

1. Introduction

Malignant brain cancer is a catastrophic disease of morbidity and mortality in adults and is the second leading cause of cancer death in children [1–7]. Despite advances in imaging technologies, the standard therapies for malignant gliomas today are largely similar to those that have been used for over five decades and generally involve maximal surgical resection followed by chemotherapy with or without radiation therapy [7–12]. About 99% of patients with glioblastoma multiforme also receive perioperative corticosteroids (dexamethasone) as part of the therapy [10]. Although dexamethasone will reduce edema and swelling associated with surgery and radiation [13], it will also elevate circulating levels of blood glucose [14,15]. Glucose is a major fuel for most glycolysis-dependent brain tumor cells and elevated glucose is associated with poor prognosis [16–19]. Radiation therapy produces oxidative tissue damage and necrosis [20–24], which will elevate glutamate levels in the microenvironment [25]. Glutamate is cytotoxic and, through the glutamate-glutamine cycle, will be rapidly metabolized to glutamine by the reactive astrocytes that surround the neoplastic tumor cells [25–27]. Glutamine is a major metabolic fuel for both brain tumor cells and tumor-associated macrophages (TAMs) [28–31]. TAMs release pro-inflammatory and pro-angiogenic factors creating a microenvironment that facilitates aggressive growth of tumor cells [32,33]. While standard therapies manage glioma growth over the short term (weeks to months), they provide an abundance of glucose and glutamine needed for rapid tumor growth and invasion. Ready access to energy metabolites will facilitate glioma recurrence and enhance growth rate over the longer term [33–35]. Indeed, the malignant phenotype of brain tumor cells that survive radiotherapy is often greater than that of the cells from the original tumor.

It is our opinion that the brain of patients with malignant gliomas should rarely be irradiated and that radiation therapy for brain cancer management is largely counterproductive to long-term patient survival [34]. This opinion does not mean that radiation therapy has no redeeming value for patients suffering malignant brain cancer. Of course radiation therapy can increase patient survival over the "no therapy" option. Radiation therapy can also be as good or better than chemotherapy alone [36]. Our point is whether radiation therapy would be better than non-toxic metabolic therapy for long-term brain cancer

Abbreviations: DR, dietary restriction; CR, caloric restriction; KD, ketogenic diet; RKD, calorically restricted ketogenic diet

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management. The issue could be settled with clinical trials where patients receive metabolic therapy in the absence of radiation therapy.

Conventional chemotherapy has faired little better than radiation therapy for the long-term management of malignant brain cancer [8,37–39]. Brain tumor chemotherapy is often associated with adverse effects that diminish the length or quality of life [12,37,38,40]. Like radiation therapy, the widely used drug temozolomide can also enhance necrotic damage in brain tissue [24]. This will contribute to the availability of glutamate and glutamine needed for tumor progression. In an initial study, bevacizumab (Avastin) with irinotecan therapy for malignant brain cancer management killed 6% of those taking the drug, while an additional 38% of patients had to discontinue use due to toxicity issues [40]. Despite the severity of these adverse effects, the investigators considered the marginal response to bevacizumab therapy superior to that of other available anti-angiogenic drug therapies. More recent studies indicate that bevacizumab enhances the invasive properties of already highly invasive brain tumors [39,41]. Indeed, bevacizumab is capable of enhancing the invasive properties of the U87-MG human glioma, which is widely recognized as a noninvasive tumor when grown as a xenograft [41]. Will it be better for patients not to take bevacizumab or to develop new drugs that inhibit bevacizumab-induced invasion? Recent studies also suggest that some anti-angiogenic compounds block chemotherapeutic drug delivery [42,43]. Viewed collectively, these findings indicate that most conventional radiation and brain cancer chemotherapies can enhance glioma energy metabolism and invasive properties, which would contribute to tumor recurrence and reduced patient survival [34].

The therapeutic targeting of brain tumor-associated mutations, while conceptually appealing, may also be problematic as hundreds of mutations can be found in tumors and not all neoplastic cells within the tumor express the same mutations [44,45]. Many targeted gene therapies suffer from the misconception that mutations cause cancer and that therapies targeting the effects of individual mutations will be effective in managing tumor growth [38,46]. These misconceptions have lead to the idea that cancer therapy can be personalized by targeting signaling pathways unique to an individual's tumor. While this therapeutic strategy could be effective for those tumors derived from germ line mutations or situations where most neoplastic cells within the tumor express the same genetic defect, most brain tumors do not arise from germ line mutations and genetic heterogeneity is common within most aggressive tumors [46,47]. Most tumor-associated mutations arise as epiphenomena of tumor progression and their association with causality and pathobiology is far from clear [33,44,48–52]. It is therefore unlikely that targeting brain tumor-associated mutations will have major therapeutic effect for most brain cancer patients.

2. Application of metabolic control theory to brain cancer management

We contend that all cancer regardless of tissue or cellular origin is a disease of abnormal energy metabolism [48]. As such, the non-toxic targeting of tumor cell energy metabolism becomes an attractive alternative to the current standard of care for brain cancer management. Principles of metabolic control theory/analysis can provide the general concepts associated with therapeutic strategies that target tumor cell energy metabolism. Basically, metabolic control analysis evaluates the degree of flux in metabolic pathways and can be used to analyze and treat complex diseases [53–60]. The approach is based on findings that compensatory genetic and biochemical pathways regulate the bioenergetic potential of cells and ultimately the phenotype. As rate-controlling enzymatic steps in biochemical pathways are dependent on metabolic environment, the management of disease phenotype depends more on the flux of the entire system than on the flux of any specific metabolic pathway or metabolite. In other words, complex disease phenotypes can be managed through self-organizing networks that display system wide dynamics involving oxidative and non-oxidative (substrate level) phosphorylation [19,48,61–64]. Global manipulations of these metabolic networks can restore orderly adaptive behavior to widely disordered states involving complex gene-environmental interactions like cancer.

As abnormal energy metabolism and biological chaos characterize brain tumors [8,19,33,65–67], general principles of metabolic control analysis can be effective for brain cancer management. This hypothesis is based on differences in energy metabolism between normal brain cells and neoplastic tumor cells. As long as brain tumors are provided a physiological environment conducive for their energy needs they will survive; when this environment is restricted or abruptly changed they will either grow slower, growth arrest, or perish [8,19]. In this review we describe how calorie restricted diet therapies, which lower circulating glucose and elevate ketone bodies (acetoacetate and β-hydroxybutyrate, β-OHB), can target brain tumors while enhancing the metabolic efficiency of normal neurons and glia. New information also suggests that ketones are toxic to some human tumor cells and that ketones and ketogenic diets might restrict availability of glutamine to tumor cells [68–70]. The success of this therapeutic strategy is also based in large part on the principles of evolutionary biology involving adaptability and variability selection. The information presented in this review has been compiled in part from information that we presented previously [8,19,71,72].

3. Adaptability and variability selection

According to Rick Potts of the Smithsonian Institution, the evolutionary success of our species has been due largely to the germ line inheritance of traits that bestowed adaptive versatility [73,74]. These traits were honed over millions of years and enabled humans to adapt rapidly to abrupt changes in the physical environment. The adaptability to abrupt environmental change is a property of the genome, which was selected for in order to ensure survival under environmental extremes. This hypothesis is an extension of Darwin's original theory (Chapter IV, Natural Selection) and can be applied to the individual cells of the organism, which exist as an integrated society of cells [75]. The success in dealing with environmental stress and disease is therefore dependent on the integrated action of all cells in the organism. Further, this integrated action depends on the flexibility of each cell's genome, which responds to both internal and external signals according to the needs of the organism. More specifically, only those cells possessing flexibility in nutrient utilization will be able to survive under nutrient stress. Environmental forcing has therefore selected those genomes most capable of adapting to change in order to maintain metabolic homeostasis [19,73–75].

The widely held notion that tumor cells are more “adaptable” or have a “growth advantage” over normal cells is inconsistent with evolutionary theory [19]. How can tumor cells that express multiple random pathogenic mutations, chromosomal rearrangements, and mitochondrial abnormalities be considered more “fit” or “advantaged” than normal cells that possess a flexible genome, normal respiratory capacity, and adaptive versatility? The answer is they are not. The issue is metabolic flexibility that is inherited through the genome verses perceived metabolic adaptability that is acquired somatically. Metabolic flexibility allows the organism to respond in a coordinated way to environmental stress according to Darwin's original theory. Although germ line changes could give some organisms a selective advantage when confronted with a novel environmental stress, most mutations reduce fitness. The genomic changes in cancer cells are not inherited in the germ line, but are acquired randomly [45,46]. Tumor cells survive in hypoxic environments not because they have inherited genes making them more fit or adaptable than normal cells, but because they have damaged mitochondria and have thus acquired the ability to derive energy largely through substrate level phosphorylation [48]. Energy through substrate level phosphorylation is required for survival in hypoxia [76–78]. Tissue macrophages can also survive in hypoxic (acidic) environments, as a part of their normal function. Do neoplastic cells have a selective advantage over tissue