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Glioblastoma: Current Chemotherapeutic Status and Need for New Targets and Approaches

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1. Introduction

Glioblastoma is the most aggressive, invasive and malignant type of glioma : a tumor which arises from the glial cells in the brain (Wrensch et al., 2002). Glioblastoma represents 54% of all the gliomas and 18% of all brain tumors (CBTRUS, 2011). It is the frequently occurring brain tumor in humans. Patients with glioblastoma usually survive 12-15 months or less after diagnosis. (Krex et al., 2007; Chandana et al., 2008).

Because prognosis for patients with glioblastoma is abysmal and current therapies for the disease are ineffective, this review critically evaluates the current chemotherapeutic status of glioblastoma and highlights the need for new therapeutic targets and approaches. The ultimate goal is to improve the outcome of glioblastoma patients.

2. Glioblastoma biology

The incidence of glioblastoma peaks with increasing age and affects adults of ages 50 to 70 (Wrensch et al., 2002). Multiple genetic mutations, upregulation or amplification of genes contribute to glioblastoma carcinogenesis. Depending on the aberrant signaling pathways involved, glioblastoma can develop either as a primary or a secondary tumor (Kleihues & Ohgaki , 1999; Ohgaki & Kleihues, 2007). Primary glioblastoma (representing >60% of all glioblastoma cases) frequently occurs in adults/older patients as a single step transformation with no clinical background. Genetic changes in primary glioblastoma include Epidermal Growth Factor Receptor overexpression (50-60%), mutations in PTEN (30%) and amplification of mdm2 gene. Secondary glioblastoma arises from a slowly progressing low grade astrocytoma or anaplastic astrocytoma to a malignant glioblastoma and affects the young population. Secondary glioblastoma patients survive longer than those with primary glioblastoma multiforme: genetic hallmark of the former group includes Tp53 inactivation (>60%) and overexpression of PDGF ligand and/or receptor. Primary and secondary glioblastomas share similar morphologies, rendering them indistinguishable (Kleihues & Ohgaki , 1999; Ohgaki & Kleihues, 2007).

3.Current therapies

3.1 Carmustine

Carmustine (BCNU) was the first tested and approved drug for treating glioblastoma: it showed modest improvement in patient survival in 1960s (Levin, 1999). Belonging to the class of nitrosoureas, it alkylates the *O*6-guanine position in the DNA and cross-links the DNA, thereby inhibiting cancer growth (Reithmeier et al., 2010). Carmustine is a lipophilic drug and crosses the blood-brain barrier (Louis et al, 2007). After being approved by FDA in 1977, it has been the mainstay of adjuvant therapy for glioblastoma (Salvati et al., 2009). When glioblastoma patients were treated with carmustine after radiation therapy, their survival improved (Brandes et al., 2004). Many still ongoing preclinical and clinical studies have also tested carmustine in combination with other chemotherapeutic drugs (Silvani et al., 2009; Reardon et al., 2004). In 2009, a study comparing temozolomide and carmustine in glioblastoma indicated that carmustine was more toxic than temozolomide alone though both had comparable efficacy (Vinjamuri et al., 2009). Combination therapies with receptor tyrosine kinase inhibitors like genistein, tryphostin and carmustine were synergisitic (Liang & Ullyatt 1998; Khoshyomn et al., 2002). Despite its use as a mainstay therapy, the survival rates of patients on carmustine alone are quite low. Short half-life, chemo-resistance, high systemic toxicity, and difficult delivery to target site, limits carmustine's effectiveness in treating glioblastoma (Johannessen et al., 2008).

3.2 Gliadel wafers

Gliadel wafers are biodegradable polymers loaded with carmustine, approved for treating recurrent glioblastoma (Panigrahi et al., 2011; Aoki et al., 2007). After glioblastoma is surgically removed, the wafers are implanted in its cavity. As the polymer is degraded, it releases the drug slowly (Panigrahi et al., 2011). In 1995, gliadel wafers showed promises because of their local action and high doses of loaded drug delivered to the target site with few off-target effects (Brem et al., 1995). Gliadel-treated patients showed median survival of 7.2 months compared to 5.4 months in the placebo group. In 2003, a randomized, placebo-controlled, multicenter, multi-national, double-blind phase 3 trial demonstrated a higher survival to risk ratio in glioblastoma patients treated with gliadel wafers, with a median survival rate of 13.9 months compared to 11.6 months in placebo controls (Westphal et al., 2003). An ongoing study adopts a multimodality approach of using gliadel wafers with other chemotherapies in glioma patients who have undergone surgery (McGirt et al., 2009). Gliadel wafer with temozolomide increased the median survival of patients with newly diagnosed glioblastoma to 21 months (McGirt et al., 2009). Although beneficial, the use of gliadel wafers for intracranial treatment of glioblastoma is complicated by edema, seizures, post-operative infections, and hydrocephalus (Gallego et al., 2007; Weber & Goebel, 2005): the complications versus benefits merits re-evaluation.

3.3 Cisplatin

In 1965, Barnet Rosenberg *et al* discovered inhibition of E. coli cell division by a platinum compound (i.e., cisplatin) formed in electrolysis of platinum electrodes (Rosenberg et al, 1965). Cisplatin was soon employed as an anticancer agent (Rosenberg et al, 1969; Williams, J.M.A Whitehouse, 1979). Cisplatin is a platinum complex with two chloride atoms and two amine groups positioned in a *cis* configuration. Once inside the body, the two chloride atoms are displaced by water molecules, the resulting hydrated complex crosslinks with

DNA strands, triggering programmed cell death (C.J. Williams, J.M.A Whitehouse, 1979). In 1980's cisplatin's efficacy on brain tumor was evaluated (Stewart et al, 1982). Although combination therapy of cisplatin with carmustine and radiation therapy was successful, patients on cisplatin therapy (with or without carmustine) developed ocular and orbital toxicities (Miller et al., 1985). Numerous other clinical trials evaluating the effectiveness of cisplatin chemotherapy in glioblastoma have demonstrated few benefits. Combination of cisplatin with temozolomide, etoposide, thalidomide, or tyrosine kinase inhibitors as a treatment option for glioblastoma have also been studied but have not significantly increased patient survival (Silvani et al., 2004; Lassen et al., 1999; Murphy et al., 2007; Nagane et al., 2007). Additionally, a phase three trial of cisplatin and carmustine administered concurrently with radiation therapy did not have significant improved outcome as compared to carmustine alone and radiation therapy (Buckner et al., 2006).

3.4 Temodar

A drug of interest since 1990, temozolomide constitutes the first line chemotherapy for treating glioblastoma following surgery and radiation (Villano et al., 2009). It is an oral alkylating agent that adds a methyl group to the O6 position of guanine residue of the DNA: the resulting methylated adduct induces apoptosis (Villano et al., 2009; Malcolm et al., 2002; Roos et al., 2007). Being lipid soluble, temzolomide shows good bioavailability and readily crosses the blood-brain barrier. In 2005, a breakthrough study demonstrated a regimen of radiation therapy followed by adjuvant and concomitant temozolomide treatment prolonged survival of glioblastoma patients compared to patients treated with radiation alone (Stupp et al., 2005). Since then it has become a standard therapy for glioblastoma with or without modifications. Combination chemotherapies of temozolomide and other drugs are in various phases of clinical trials but none showed benefits compared to temozolomide treatment alone (Ren et al., 2009). One of the major drawbacks of temozolomide therapy is recurrence of glioblastoma. The lesion produced in the DNA by temozolomide could be corrected by the repair enzyme O6 methyl guanine DNA methyl transferase, encoded by the MGMT gene (Sarkaria et al., 2008). Response rates to temozolomide therapy depend on the transferase activity and cancers with high levels of MGMT activity gradually acquire resistance to temozolomide (Nagane et al., 2007). The promoter methylation status of MGMT governs a drug's efficacy towards the tumor. Patients with an increased % of MGMT methylation respond more favorably to temozolomide treatment (Hegi et al., 2008). Drugs mimicking this enzyme are being tested in combination with temozolomide to prevent MGMT actions. One such drug is O6 benzylguanine, which acts as a pseudo-substrate to MGMT enzyme (Kaina et al., 2010; Dolan & Pegg, 1997). However, due to its dose-related hematologic toxicity, its use in combination with alkylating agents is still under investigation (Dolan & Pegg, 1997; Quinn et al., 2009). A recent study showed that patients with unmethylated MGMT tumors benefitted from the combination of interferon β and temozolomide, as compared to patients who received temozolomide alone, highlighting the role of interferon β and also suggesting that methylation status of MGMT is not a sole parameter controlling treatment outcome (Motomura et al., 2011). Tumor resistance to temozolomide as with other alkylating agents is a common phenomenon seen in patients with glioblastoma. Apart from MGMT, many studies have shown that resistance to temozolomide is mutlifactorial (Sarkaria et al., 2008). Strategies to overcome this resistance

have been analyzed in order to improve temozolomide's activity against glioma and other cancers (Sarkaria et al., 2008; Tentori & Graziani , 2002). With greater understanding of diverse mechanisms responsible for imparting resistance to cancer cells and the role played by growth factor receptors in glioblastoma tumorigenesis, new therapies in combination with temozolomide are being evaluated. Such combination therapies include use of protein tyrosine/serine-threonine kinase inhibitors and temozolomide (Chaponis et al., 2011; Guillard et al., 2009; Peereboom et al., 2010). Though some studies demonstrated beneficial effects, others have reported greater toxicity. Thus, as a promising drug for treating glioblastoma, temozolomide only modestly enhances patient survival. There is a need to find other small molecules with efficacy and safety profiles superior to those of current therapies to be targeted to glioblastoma therapy.

4. Potential drug targets and new therapies

4.1 Epidermal growth factor receptor (EGFR) and cellular signaling pathways

EGFR plays a critical role in cancer progression and invasion. Present in all germ layers, EGFR is activated by several ligands including EGF. Binding of EGF results in homodimerization and/or heterodimerization with other members of the EGFR family (HER2, HER3 and HER4), leading to tyrosine phosphorylation of its cytoplasmic domain. This activation initiates a series of signaling pathways resulting in cell division. In cancer cells, mutations or amplification of EGFR leads to uncontrolled cell proliferation (Yarden, 2001). Activation of EGFR leads to activation of downstream elements such as phosphatidylinositol-3 kinase (PI3K), which converts phosphatidylinositol diphosphate (PIP_2) to phosphatidylinositol triphosphate (PIP_3). Protein kinase B or AKT binds the PIP3 with the pleckstrin homology (PH) domain, resulting in phosphorylation of AKT at threonine 308 and serine 473 sites. Phosphorylated AKT leads to cell growth, motility and proliferation by activating several downstream signaling pathways (Chakravarti et al., 2004).

PTEN/MMAC/TEP-1, (Phosphatase and tensin homologue deleted on chromosome ten/mutated in multiple advanced cancer/Transforming growth factor β regulated and epithelial cell enriched phosphatase) a tumor suppressor gene located on chromosome 10 is mutated in gliomas. PTEN dephosphorylates PIP3 to PIP2 in the PI3 kinase pathway and acts as a negative regulator of this pathway (Cheng & Nicosia, 2001). Continuous activation of PI3K/Akt pathway is associated with malignant transformation of cells. Activation of PI3K pathway and mutations in PTEN occur frequently in GBM tumors when compared to non-GBM tumors (Chakravarti et al., 2004).Mammalian target of rapamycin (mTOR) is a serine/threonine kinase known to function downstream of PI3K/Akt pathway. Akt activates mTOR through inhibition of TSC1/2 complex and activation of Ras homologue-enriched in brain (Rheb). mTOR regulates translation initiation through two pathways – eukaryotic translation initiation factor (eIF4E) binding proteins (4EBP1) and ribosomal p70 S6 kinase (p70S6K) (Hay & Sonenberg, 2004).Inhibition of signaling pathways generated by activation of EGFR are important targets to develop new drugs for the treatment of glioblastoma because EGFR is amplified and overexpressed in such tumors (Lo, 2010; Penar et al., 1997).

4.2 PLCγ1

Phospholipase C gamma one (PLCγ1) is an enzyme important in cell signaling. In its phosphorylated active form, it cleaves the membrane phospholipid, phosphatidylinositol 4,

5 biphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3). IP3 increases intracellular calcium stores. DAG together with calcium activates protein kinase C which further participates in signal transduction pathways (Kim et al., 2000). Growth factor receptor activation is an important mediator of PLCγ1 phosphorylation and functioning. Overexpression of epidermal growth factor receptors (EGFR) in glioblastoma multiforme (GBM) promotes PLCγ1 activation (Chen et al., 1994; Yang et al., 1994; Wahl et al., 1992). Many functions attributed to PLCγ1 activation include proliferation, differentiation, cell motility and invasion of tumor cells (Jones et al., 2005; Wells & Grandis, 2003). Furthermore, PLCγ1 is associated with breast cancer metastasis and is highly expressed in breast cancer tissues (Arteaga et al., 1991). Activation of PLCγ1 by tyrosine kinase receptors mediates actin cytoskeleton rearrangement, through release of actin modifying proteins gelsolin, profilin, myosin type I (Chen et al., 1996). In the resting state, these proteins are bound to PIP2 and participate in cell motility only when they are released during hydrolysis of PIP2 by PLCγ1. Thus, this mechanism defines the role played by the enzyme in cell motility and invasion (Chen et al., 1996). Molecular inhibition of PLCγ1 is associated with decreased invasion in gliomas, prostate, breast and bladder carcinomas (Turner et al., 1997; Katterle et al., 2004; Khoshyomn et al., 1999). A chemical inhibitor of PLCγ1, U73122 inhibits invasion of glioblastoma cells into co-cultured fetal rat brain aggregates (Khoshyomn et al., 1999). During invasion, tumor cells undergo a series of steps to proliferate and thrive locally (Tysnes & Mahesparan, 2001). Thus, these functional considerations of the role of PLCγ1 in glioblastoma proliferation and invasion strongly suggest PLCγ1 could be a drug target.

4.4 Invasion

The characteristic feature of glioblastoma, which makes it a lethal disease, is its propensity to invade surrounding normal brain tissues (Giese et al., 2003). Unlike other cancers, glioblastoma does not metastasize to distinct organs but infiltrates peritumoral regions (Giese et al., 2003; Nakada et al., 2007). Glioblastoma patients show poor survival because of the inability of current therapies to control the aggressively invasive glioblastoma, which is spurred on by autocrine and paracrine factors released from the tumor and its microenvironment, respectively (Hoelzinger et al., 2007). Overexpression and activity of the epidermal growth factor receptors in almost all glioblastomas is responsible for signaling pathways leading to invasion (Guillamo et al., 2009). These signals help the cancer cells to detach from the bulk of the tumor and adhere to the extracellular matrix components of other cells. The latter process follows only when the tumor invades through the matrix to the surrounding brain parenchyma. Thus, during invasion, a family of proteases known as the matrix metalloproteases and urokinase plasminogen activator receptor system play an active role (VanMeter et al., 2001; Mohanam et al., 2001). Being soluble zinc-dependent enzymes and secreted as inactive zymogens (pro-MMPs) (Visee & Nagase, 2003), matrix metalloproteases (MMPs) cleave the basement membrane and extracellular matrix components like collagen, fibronectin, laminin, and vitronectin. They help in tissue remodeling, angiogenesis, and metastasis (VanMeter et al., 2001). Out of the 24 members in the MMP family, only two forms are overexpressed in glibolastoma and their expression correlates with the degree of malignancy and poor survival rate (Deryugina et al., 1997; Choe et al., 2002). These two forms are MMP-2 (72 kDa type IV collagenase or gelatinase A) and MMP-9 (92 kDa type IV collagenase or gelatinase B) and differ from other members in their substrate preference. Some metalloproteases are not secreted but are expressed on the

surface of tumor cells. MT1-MMP (membrane bound matrix metalloprotease-1) is one such protease which is upregulated in glioblastomas. A major role of MT1-MMP is in the cleavage of pro-MMPs to active MMPs at the cell surface. Together with MMP-2, and MMP-9, MT1-MMP imparts an invasive phenotype to glioblastoma multiforme (Fillmore et al., 2001; Nakada et al., 2001). Urokinase plasminogen activator and receptor (uPA/uPAR) system is important in cancer cell migration and invasion (D'Alessio & Blasi, 2009; Duffy, 2004). Once this system is activated, it converts the inactive plasminogen to the active plasmin. Plasmin degrades the extracellular matrix components (D'Alessio & Blasi, 2009). Increased expression of uPAR on the surface of glioblastoma correlates with poor prognosis. In contrast with normal brain tissue, high grade gliomas (i.e., glioblastoma) exhibit increased activity of the uPA/uPAR system (Mohanam et al., 1998; MacDonald et al., 1998). This system can also activate cell proliferation pathways by interacting with other proteins like vitronectin and integrins (Sidenius & Blasi, 2003).Many studies and clinical trials are now focusing on anti-invasive chemotherapies as a treatment option for glibolastoma. Apart from synthetic derivatives, natural compounds in soy, curcumin can also inhibit glioblastoma invasion *in vitro* (Puli et al., 2006; Senft et al., 2010). Their activity *in vivo* warrants further research. Since a vast signaling network is aberrant in glioblastoma, therapies directed toward a single target cannot be expected to lead to positive outcomes. For example, one clinical trial showed marimastat to be ineffective in increasing survival of patients post-radiosurgery (Levin et al., 2006). Consequently, combination therapies targeting invasion and other pathways in glioblatoma are still ongoing.

4.5 Angiogenesis

Angiogenesis, the process of formation of new blood vessels from existing blood capillaries, is one major contributor to glioblastoma multiforme carcinogenesis and helps the tumor cells to flourish (Tate & Aghi, 2009). To maintain the demand of food, nutrients, and oxygen, tumor cells recruit new blood vessels from those already present (Folkman, 1971; Tate & Aghi, 2009). Likewise, malignant gliomas are highly vascularised and have an angiogenic phenotype (Jain et al., 2007). Angiogenesis takes place with the over-expression of angiogenic factors or when the angiogenic imbalance strikes. One growth factor involved is vascular endothelial growth factor (VEGF), which promotes formation of endothelium in normal cells (Kargiotis et al., 2006). In glioblastoma, VEGF-a, a pro-angiogenic factor from the VEGF family, plays a crucial role in angiogenesis. VEGF-a is secreted in large amounts by glioblastoma cells and can elicit responses like extracellular matrix degradation, endothelial cell proliferation, and expression of other angiogenic factors such as urokinase type plasminogen activator, plasminogen activator inhibitor-1 and matrix metalloproteases (Plate et al., 1992). Secreted VEGF stimulates angiogenesis by binding to specific tyrosine kinase VEGF receptors on endothelial cells of blood vessels surrounding the tumor and initiates proliferation of endothelial cells, thereby ensuring the metabolic demands of the growing tumor are adequately met. There are other pro-angiogenic factors like angiopoetins, IL-8, hepatocyte growth factors, endothelins that are expressed by glioblastoma cells when the “angiogenic switch” is turned on: all these factors have functions similar to that of VEGF in promoting angiogenesis (Argyriou et al., 2009). Some new treatment strategies for GBM include targeting VEGF/VEGF receptors (VEGFR) by monoclonal antibody or VEGFR traps, respectively (Beal et al., 2011). Approved by FDA in 2009 for treating recurrent glioblastoma, bevacizumab (Avastin) is a humanized monoclonal

antibody against VEGF-a (Beal et al., 2011). Bevacizumab decreases tumor blood vessel density and remodels tumor vasculature in a neuroblastoma xenograft model (Dickson et al., 2007). The National Cancer Comprehensive Network recommends bevacizumab with or without other chemotherapy in case of glioblastoma recurrence (National Comprehensive Cancer Network clinical practice guidelines in oncology-central nervous system cancers. v.1.2010). Combination chemotherapy of bevacizumab with irinotecan shows favorable results in phase 2 trials of recurrent malignant glioma (Vredenburgh et al., 2007). Clinical trials are on-going for using bevacizumab in new cases of glioblastoma (Lai et al, 2010). Inclusion of anti-angiogenic therapies to cancer treatment is favorable, because they facilitate increased penetration of conventional chemotherapies and show better response rates (Jain, 2001). Other than bevacizumab, anti-angiogenic agents in various phases of clinical trials include cediranib, cilengitide, and aflibercept (Batchelor et al., 2010; Reardon et al., 2008; Wachsberger et al., 2007). Though favorable responses and anti-tumor effects occur with combination of various anti-angiogenic agents in different cancer models, efficacy of bevacizumab monotherapy in increasing glioblastoma patient survival has not transpired. Emergence of an invasive phenotype while angiogenesis is being targeted in glioblastoma constitutes a major limitation of anti-angiogenic monotherapies (Lamszus et al., 2003; Verhoeff et al., 2009; Keunen et al., 2011). Thus, improved therapies need to be developed to target glioblastoma.

4.6 Metabolism

Metabolic and other functional roles of astrocytes under physiological conditions: In mammalian nervous system, neurons and astrocytes are intimately and functionally interrelated: astrocytes play key roles in neurotransmitter and substrate cycling in conjunction with neurons (Chowdhury et al., 2007; Hertz et al., 2007). Moreover, astrocytes protect neurons against various pathophysiological assaults (e.g., oxidative stress, ammonia toxicity) (Dukhande et al., 2006; Wong et al., 2010). However, to what extent these physiological roles are still assumed by astrocytes once they are transformed into astrocytomas has not been elucidated. Nevertheless, recent new evidence suggests that cancer cells, and to a lesser known extent astrocytomas too, exhibit metabolic adaptation and other phenotypic alterations that allow them to survive, proliferate, and invade into their surrounding space occupied by normal cells/tissues (Bhardwaj et al., 2010; Lino & Merlo, 2009; Ordys et al., 2010; Semenza, 2011; Stegh et al., 2008).

Metabolic adaptation and/or reprogramming in cancer cells in general and astrocytoma/glioblastoma in particular: As early as the 1920's, Otto Warburg and his associates were the first to note that cancer cells appear to depend on glycolysis for energy production and survival even though oxygen is not in short supply. (Warburg et al., 1927). Warburg's extensive investigation into the metabolic characteristics of multiple types of cancer cells prompted him to hypothesize that cancer cells reply on glycolysis for energy supply because their mitochondrial oxidative metabolism is dysfunctional (Warburg, 1956). His hypothesis has been neglected for some 80 years until the recent resurgence of interests in "the role metabolic reprogramming in cancer progression" (Semenza, 2011). The recent "renaissance of the Warburg Hypothesis" (Warburg et al., 1927, Warburg, 1956) has stimulated a new era in elucidating the aggressive nature of many malignant tumors (including glioblastoma) and their purported dependence on glycolysis for energy and survival (Bhardwaj et al., 2010; Lino & Merlo, 2009; Ordys et al., 2010; Semenza, 2011; Stegh

et al., 2008). While numerous studies have documented mutations in mitochondrial DNA (mtDNA) in a variety of cancers (Czarnecka & Bartnik, 2009) can thus tentatively provide a mechanistic connection to dysfunctional mitochondrial oxidative metabolism as predicted by the Warburg hypothesis, other recent evidence suggests this aspect of the Warburg hypothesis requires critical re-appraisal (Bayley & Devilee, 2010; Dang et al., 2011; Frezza et al., 2011; Ordys et al., 2010; Srivastava & Moraes, 2009).

The aspect of the Warburg hypothesis emphasizing dysfunctional mitochondrial oxidative metabolism in cancer cells deserves a critical re-appraisal because recent studies on cancer cell metabolism have uncovered new mechanistic roles for mTOR and p53. These mechanistic roles are new additions to the already established role of mTOR in tumor development and progression and the fact that in over 50% of the cancer types, p53, a tumor-suppressor, is mutated and their p53 mutation is associated with either decreased apoptosis and/or enhanced proliferation potential in those cancers. Earlier, we have already discussed the importance of these two phenotypic characteristics of glioblastoma.

mTOR complex 1 (mTORC1) is aberrantly activated in many human cancers thereby positioning it to modulate on metabolic changes common to cancer cells (Yecies & Manning, 2011). Furthermore, recent characterization of the metabolism of cancer cells reveals that, mTORC1 activation is adequate to promote an increase in glucose uptake, glycolysis, and lipid synthesis in addition to the pentose phosphate shunt pathway (Ramanathan & Schreiber, 2009; Yecies & Manning, 2011). Because these are all metabolic phenotypes of cancers, mTORC1 has emerged as a central relay for various oncogenic signaling pathways and their convergence in regulating metabolism in cancer cells (Yecies & Manning, 2011). The finding that mTOR functions as a positive regulator of hypoxia-inducible factor 1 (HIF-1) activation by hypoxia (Hudson et al., 2002) highlights the importance of mTOR in regulating signals that lead mammalian cells, especially cancer cells, to adapt to oxygen- and nutrient-poor environments. Furthermore, mTOR is known to exert a direct control of mitochondria (Ramanathan & Schreiber, 2009). Thus, these new mechanistic roles of mTOR strengthen the notion we have discussed earlier that mTOR exhibits good potential as a target for new anti-cancer drug discovery. There has been increasing evidence demonstrating that p53 can regulate multiple metabolic pathways. p53 contributes to the regulation of glycolysis, oxidative phosphorylation, glutamine catabolism, synthesis of nucleotides, fatty acid oxidation, insulin sensitivity, mitochondrial integrity, antioxidant response, autophagy, and mTOR signaling (Maddocks & Vousden, 2011). Inactivation of p53 in cancer cells promotes the Warburg effect as p53 suppresses glycolysis and promotes oxidative phosphorylation. However, there are some known but complex cross-talks between the signaling pathways regulated by mTOR and p53 (Maddocks & Vousden, 2011): nevertheless, whether the interactions between mTOR and p53 signaling favor glioblastoma cell growth and proliferation remains to be fully elucidated.

Some recent cancer cell metabolism studies have further challenged the reliance of cancer cells on glycolysis for energy production and lipid synthesis: in fact, such studies have argued that glycolysis alone is inadequate to maintain the metabolic needs of growing and actively dividing cancer cells (Dang et al., 2011; Maddocks & Vousden, 2011; Shanware et al., 2011). Thus, many researchers have re-discovered the importance of glutamine in meeting the inadequacy of glycolysis to fuel growth and proliferation of many cancer types including gliomas (Dang et al., 2011; Maddocks & Vousden, 2011; Shanware et al., 2011). In this context, as alluded to above, neuroscientists have long recognized the importance of glutamine in astrocytic metabolism and astrocytes-neurons metabolic and neurotransmitter

cycling (Chowdhury et al., 2007; McKenna, 2007). Consequently, these recent interests in the role of glutamine in cancer cell metabolism call into question the need to better appreciate the metabolic and neurotransmitter cycling roles of glutamine in glioblastomas. Because these roles in glioblastomas are poorly understood, these knowledge gaps prompted us to consider the appropriate techniques and approaches to allow the acquisition of this knowledge. Indeed, the recent rapid advances in magnetic resonance imaging (MRI) and nuclear magnetic resonance (NMR) spectroscopy provide exciting new possibilities in this area of research and development.

Technological advances that can be exploited to diagnose and/or treat glioblastoma:MRI and other imaging techniques in diagnosing glioblastoma: Recent advances in magnetic resonance imaging (MRI) and related imaging techniques have opened new possibilities in the differential and more accurate clinical assessment of brain tumors including glioblastomas (Cha, 2009; Lemort et al., 2007; Wang & Lam, 2008). Historically, uses of MRI in the diagnosis of brain tumors were initially focused on neuromorphological demonstration, confirmation, and localization of brain tumors. However, the rapid advances of MRI, functional MRI, and magnetic resonance spectroscopy (MRS) spectroscopy in the last decade have allowed the diagnostic imaging of neurotumors combining the use of physiology-based imaging methods that complement the more traditional morphology-based imaging protocols. For example, "High-resolution spectroscopic imaging may contribute to pre-therapeutic grading and characterization of gliomas, as can diffusion techniques. The latter also hold promise in predicting survival in malignant supratentorial astrocytoma and could help to define areas for biopsy. Both methods can differentiate recurrent tumour from radiation injury. Perfusion-weighted magnetic resonance techniques offer potential markers of tumour angiogenesis and capillary permeability, and correlate well with vascular endothelial growth factor expression in grade II and grade III tumours. Functional magnetic resonance imaging can assess whether surgical treatment is feasible and select patients for intraoperative cortical stimulation" (Lemont et al., 2007).

Recently, use of the nanoparticles in the diagnosis and detection of cancers, including glioblastomas, has gained much impetus because of putative enhancement involving their applications in MRI (Bhushan et al., 2010; Cole et al., 2011). The advances in development of newer cancer imaging and therapies based on metallic nanoparticles may help in early detection of cancer and thus contribute to decreasing deaths due to cancer. Various cancer imaging and therapies based on use of metallic nanoparticles are at different stages of preclinical and clinical development. Nanoparticles composed of iron oxide nanoparticles, zinc oxide nanoparticles, gold nanoparticles, silver nanoparticles, and cerium oxide nanoparticles have tremendous potentials to be developed as novel diagnostic and therapeutic agents in cancer (Bhushan et al., 2010; Jain 2010). Furthermore, enhanced cancer biomarker and genetic mutation detection techniques would help in identifying individuals at high risk for developing cancer. In this context, multi-functional metallic nanoparticles show exciting therapeutic potentials and these are currently under development for cancer therapy to be clinically applied in the near future. Metallic nanoparticles can be engineered to enhance the efficacy of current diagnostic and imaging techniques in cancer (Bhushan et al., 2010). Clearly, with the explosive advances in the design and applications of new metallic nanoparticles, this application area in cancer diagnosis and assessment shows exciting new potentials.

Technological advances that can be exploited to treat glioblastoma: As already alluded to above, the recent "renaissance of the Warburg Hypothesis" has stimulated much research into cancer cell metabolism (Bhardwaj et al., 2010; Lino & Merlo, 2009; Ordys et al., 2010; Semenza, 2011; Stegh et al., 2008). Indeed, the presumed dependence of cancer cells on glycolysis for cancer cell growth and proliferation has prompted much new investigation into exploring the glycolytic pathway as a new target for anti-cancer drug discovery (Bhardwaj et al., 2010; Chatterji et al., 2007; Chatterji et al., 2009; Lai et al., 2008; Lino & Merlo, 2009). We have demonstrated that two glycolytic enzyme inhibitors, 3-bromopyruvate and iodoacetate, showed efficacy in lowering the survival of pancreatic cancer (Bhardwaj et al., 2010) and glioblastoma U87 (Chatterji et al., 2007; Chatterji et al., 2009; Lai et al., 2008) cells. Thus, our studies strongly suggest that glycolytic enzyme inhibitors exhibit proof-of-concept potential in discovering new anti-cancer drugs (Bhardwaj et al., 2010; Chatterji et al., 2007; Chatterji et al., 2009; Lai et al., 2008). Consistent with our findings (Bhardwaj et al., 2010; Chatterji et al., 2007; Chatterji et al., 2009; Lai et al., 2008) are the results of human clinical trials employing 2-deoxyglucose (2-DG) in combination therapy with radiation for treatment of glioma (Prasanna et al., 2009). An inhibitor of glucose transport and glycolysis, 2-DG reportedly enhances the effects of radiation in inducing glioma cell death (Prasanna et al., 2009). Thus, the glycolytic pathway in glioblastoma constitutes an excellent target for further anti-cancer drug discovery studies. Nevertheless, because the prognosis of patients diagnosed with glioblastoma is abysmal, there is an urgent need to more fully elucidate the metabolic phenotype of glioblastomas along with exploring glycolysis as a target for discovering new anti-cancer drugs.

Magnetic resonance spectroscopy to elucidate metabolic adaptations/alterations in glioblastoma: High lactate accumulation, despite adequate oxygen availability, is a metabolic pattern commonly associated with malignant transformation of the uncontrolled dividing cell. This metabolic phenotype, termed aerobic glycolysis and historically known as the Warburg effect, is characterized by high glycolytic rates and reduced mitochondrial oxidation (Bhardwaj et al., 2010; Lino & Merlo, 2009; Ordys et al., 2010; Semenza, 2011; Stegh et al., 2008), features that favor cell survival in the hypoxic microenvironments found in tumors. This phenotype also favors the routing of key metabolic intermediates away from oxidative metabolism and toward anabolic processes required by rapidly dividing cells (McFate et al., 2008). However, the mechanistic relationship between altered glucose metabolism and malignancy remains poorly understood due to prior lack of appropriate techniques to study such phenomena. MRS has become a major tool in the non-invasive characterization of brain tumor metabolism *in vivo* and *in vitro*. A highly versatile technique, MRS allows measurements of the concentrations of many neurochemicals, including the kinetics of single enzyme-catalyzed reactions such as LDH (Xu et al., 2007) or creatine kinase (Smith et al., 1997), as well as the rates of entire metabolic pathways, such as the TCA cycle and the glutamate/glutamine neurotransmitter cycle (Sibson et al., 2001; de Graaf et al., 2003). MRS is commonly employed with several stable (non-radioactive) isotopes of biological importance such as ^{1}H, ^{13}C, ^{15}N, and ^{31}P, allowing investigation of many aspects of cellular metabolism. Of these nuclei, only ^{1}H and ^{31}P exist at ~100% natural abundance, thus requiring no specific enrichment prior to their measurement. Because ^{13}C exists at low natural abundance (~1.1%), selective enrichment of ^{13}C in appropriate substrates allow its use as a metabolic tracer. The high chemical specificity of ^{13}C MRS, which can distinguish ^{13}C isotope incorporation into not only different molecules, but also specific carbon positions

within the same compound, allows the fate of the ^{13}C label into and through multiple metabolic pathways to be followed (Zwingmann and Leibfritz, 2003). Until recently the low sensitivity of ^{13}C detection (and correspondingly large detection volume) has precluded its use for *in vivo* imaging of tumors, although with the advent of Dynamic Nuclear Polarization (DNP) and hyperpolarized biomarkers of tumor metabolism (see below), direct ^{13}C detection could become a major tool in tumor staging and response to targeted therapies.

As discussed above, brain tumors such as gliomas produce increased amounts of lactate, which can be measured by ^{1}H MRS (Kaibara et al., 1998; Herholz et al., 1992; Terpstra et al., 1998; McKnight, 2004). Glucose production of lactate through glycolysis, whether produced anaerobically (hypoxia) or aerobically, can be determined from the change in lactate concentration verses time in a series of sequentially acquired ^{1}H or ^{13}C NMR spectra. Lactate can be measured either without isotopic labeling (e.g., by differencing of ^{1}H spectra or by use of selective lactate-editing techniques), or with ^{13}C isotopic enrichment of the precursor glucose pool, and both approaches have their specific advantages depending on the desired information. With ^{13}C isotopic enrichment additional MRS techniques can be employed, such as direct ^{13}C detection with ^{1}H-decoupling to enhance sensitivity and resolution, or direct ^{1}H detection with ^{13}C-editing to differentiate ^{13}C-labeled from unlabeled proton resonances, so-called heteronuclear ^{1}H-[^{13}C] MRS. Because the heteronuclear ^{13}C-edited ^{1}H differencing technique (Fitzpatrick et al., 1990) permits both labeled and unlabeled species to be measured from a single set of acquired spectra, the fractional enrichment of lactate-C3 reflects the sum of the pathways contributing carbon atoms (both ^{13}C and ^{12}C) to the C3 position of lactate.

The use of heteronuclear ^{1}H-[^{13}C] MRS to characterize the C6 glioma metabolic phenotype (high glycolysis and low oxidation) was elegantly demonstrated for the rat brain *in vivo by* Terpstra et al., (1998). These authors found that the glioma metabolized glucose to lactate increased lactate turnover and reduced oxidative metabolism of glucose by the reduced incorporation of ^{13}C label in glutamate, which is a measure of TCA cycle flux. ^{1}H and $^{1}H/^{13}C$ heteronuclear MRS methods have also been used to study glioma biopsies *ex vitro* (Barton et al., 1999; Martínez-Bisbal et al., 2004) and glial-derived tumor cell lines in vitro (Portais et al., 1993; Serkova et al., 1996; Lehtimäki et al., 2003). In ongoing studies in our laboratory, we incubated cultured human glioblastoma U87 cells with [1,6-$^{13}C_2$]glucose as a tracer and measured the metabolite profiles in extracts of these cells using ^{1}H-[^{13}C] MRS (Fig. 1). The extract spectra revealed high levels of lactate, with lower levels of glutamate and alanine, as well as other substances not yet identified. Inspection of ^{13}C labeled metabolites revealed substantial turnover of lactate-C3 (percentage enrichment, ~31%) compared to a lower enrichment in glutamate-C4 (~14%), consistent with a more glycolytic (and less oxidative) metabolic phenotype. The high glycolytic and low oxidative rates displayed by gliomas suggest these pathways as potential therapeutic targets, as emphasized in several reports (Mathupala et al., 2010).

More recently, the introduction of hyperpolarized MRS, which increases the detection sensitivity of an NMR-active nucleus up to 10,000 times, has generated intense excitement in the possibility of imaging low concentration metabolites. Special techniques are employed to achieve hyperpolarization, although the lifetime is brief, decaying according to the spin-lattice relaxation time. Thus, ^{13}C in carbonyl groups, which exhibit long T1's (many tens of seconds) can be suitable employed as metabolic probes. Particularly promising as a

biomarker of tumor metabolism has been the development of hyperpolarized ^{13}C-labeled substrates such as [1-^{13}C]pyruvate (Kurhanewicz et al., 2011). Tumors express high amounts of LDH, which catalyzes a rapid exchange between pyruvate and lactate. The rapid appearance of hyperpolarized [1-^{13}C]lactate can thus serve as an indirect measure of LDH activity and tumorgenicity. Additional metabolic products are seen, such as [1-^{13}C]alanine, resulting from alanine transaminase, and $H^{13}CO_3$, arising through decarboxylation by pyruvate dehydrogenase and subsequent hydration by carbonic anhydrase. Reduced $H^{13}CO_3$ reflecting reduced TCA cycle flux can also be used as a biomarker of tumor mitochondrial metabolism (Terpstra et al., 1998). The method was recently applied to the study of human glioblastoma xenografts in rats (Park et al., 2010) and glioblastoma cells and murine xenografts *in vitro* and *in vivo* to follow the effects of an inhibitor (and anticancer agent) of phosphotidylinositol-3-kinase on tumor growth (Ward et al, 2010). For studies of brain tumors, hyperpolarized molecules such as [1-^{13}C]pyruvate and other substrates may prove particularly useful because the blood-brain-barrier, which normally restricts the passage of substrates, is disturbed during tumor growth, allowing for faster uptake and more time for metabolism prior to the decay of polarization.

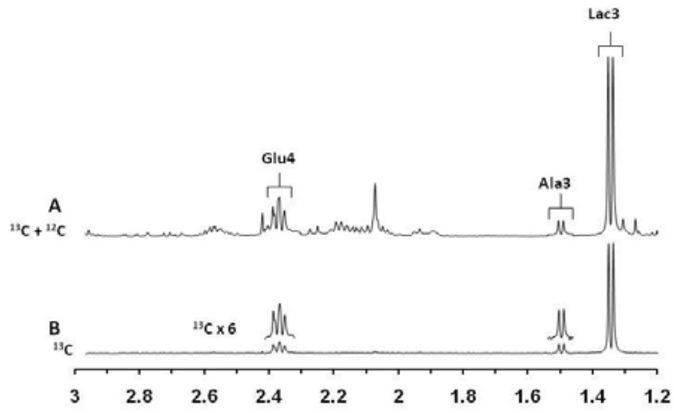

Fig. 1. Representative *in vitro* ^1H-[^{13}C]-NMR spectra of extracts of U87 glioblastoma cell pellet after 30 min incubation of [1,6-$^{13}C_2$]glucose(10 mM): (A) Total metabolite intensity representing the sum of ^{12}C and ^{13}C; (B) ^{13}C-labeled metabolites arising during [1,6-$^{13}C_2$]glucose infusion (10 mM: 30 min incubation). Highlight (x6) areas of Glu and Ala ^{13}C-labeled metabolites. Abbreviations: Glu4, glutamate-C4; Ala-C3, alanine-C3 and Lac3, lactate-C3. Spectra were scaled independently to enhance visual clarity owing to the lower amino acid levels observed in U87 glioblastoma cell pellet.

4.7 MicroRNA approach

Gene expression can be regulated by microRNAs. MicroRNAs are 19-25 nucleotides long and are capable of inhibiting translation and mRNA degradation thereby blocking protein production. microRNAs are named by numbers and the number reflects the sequence when they are identified. The next microRNA discovered will be the next number. Also mature microRNAs are named as miR whereas the primary transcript is named as mir. They influence multiple processes in several diseases including cancer (Mendell, 2005). In cancer, their effects are found in invasion, migration and metastasis (Nana-Sinkam & Croce, 2011). They play roles as oncogenes and tumor suppressor genes in several cancer types. Each

miRNA can affect several genes and each gene can be regulated by several microRNAs. The relationship between the target RNA and microRNA in regulating many pathological states is emerging (Perron et al., 2007). Thus, it is timely to investigate the impact of microRNAs in glioblastoma invasion and migration and apply this knowledge in mapping cancer therapeutic strategies. An emerging role of microRNA in resistance may be attributed to its effect on MDR. MicroRNAs mR-27a, miR-451 and miR-138 are known to impact response to chemotherapeutic drugs in several cancers including esophageal, breast, and ovarian cancers and leukemia (Hing et al., 2010; Li et al., 2010; Zhao et al., 2010; Kovalchuk et al., 2008). P-glycoprotein is present in the blood-brain barrier and may be regulated by miR-27a and miR451 (Zhu et al., 2008). In glioblastoma, 10 different miRNA were identified and shown to be predictor of prognosis (Srinivasan et al., 2011). In addition, miR-10b (Gabriely et al., 2011) has been implicated in progression of gliomas. MiR-101 that regulates PcG protein EZH2, a histone methyltransferase, may play a role in glioblastoma progression (Smits et al, 2010). Other microRNA's implicated in glioblastoma progression are listed in Table 1.

4.8 Isoflavones

Micronutrients may be employed as chemopreventive agents: they may be employed to suppress or reverse carcinogenesis, thereby preventing the development of cancer. "Micronutrients include any dietary substance, essential or non-essential that are present in small amounts and brings about a physiological effect" (Greenwald et al., 2002). Example of micronutrients include, but are not limited to, vitamins, minerals, soy phytoestrogens, and other phytochemicals (Russo et al., 2005). Isoflavones are phytoestrogen compounds highly enriched in soy and exhibit anticancer properties. Epidemiological studies have demonstrated that Asian population consuming diets rich in isoflavones show lower incidences of hormone-related cancers (Lee et al., 1991). Genistein (4', 5, 7-trihydroxyisoflavone) and biochanin A (4'-methoxy, 5, 7-dihydroxy isoflavone) are natural isoflavonoid phytoestrogens and are found in soy and subterranean clover, respectively (Persky & Van Horn, 1995). Genistein is a well studied chemopreventive agent (Taylor et al., 2009; Sarkar & Li, 2002). Genistein exerts its anti-cancer properties via several mechanisms: inhibition of tyrosine phosphorylation, weak estrogenic and anti-estrogenic properties, as an anti-oxidant, inhibition of topoisomerase II, inhibition of angiogenesis, and induction of cell differentiation in breast cancer cells (Barnes & Peterson, 1995; Fotsis et al., 1993; Messina et al., 1994). Genistein also competes with ATP for binding to the tyrosine kinase domain, thereby inhibiting tyrosine kinase-mediated signaling processes (Chen et al., 2003). Our work in an *in vitro* co-culture model showed genistein inhibits glioblastoma invasion by inhibiting EGFR tyrosine kinase activity (Penar et al., 1997; Penar et al., 1998). Biochanin A has inhibitory potential on lung tumor development in mice induced by benzo(a)pyrene (Lee et al., 1991). Both genistein and biochanin A inhibit serum- and EGF-stimulated growth of human prostate cancer cells (Peterson & Barnes, 1993; Hempstcok et al., 1998). Biochanin A also inhibits the incidence and growth of xenograft tumors in athymic mice subsequent to injection of prostate cancer cells (LNCap) into the mice (Rice et al., 2002). We have demonstrated that both genistein and biochanin A inhibit invasion of glioblastoma cells by lowering the expression and activity of matrix-degrading enzymes (Puli et al., 2006). Soy isoflavones appear to be safe and effective in pre-clinical studies but clinical trials supporting their efficacy are still required (Virk-Baker et al., 2010).

MICRO RNA	FUNCTIONAL EFFECTS	REFERENCES
miR-7	EGFR, Akt pathway	Kefas et al., 2008
miR-10b	Resistance, Invasion	Ujifuku et al., 2010; Sasayama et al., 2009
miR-21	Apoptosis, EGFR, Tumor suppressor, MMP, Resistance	Shi et al., 2010; Ren et al., 2010; Zhou et al., 2010; Li et al., 2009; Conti et al., 2009; Chen et al., 2008; Papagiannakopoulos et al., 2008; Gabriely et al., 2008; corsten et al., 2007; Chan et al., 2005
miR-34a	Oncogenes	Li et al., 2009; Li et al., 2009
miR-93	Angiogenesis, tumor growth	Fang et al., 2011
miR-124a	Migration, Invasion	Fowler et al., 2011; Silber et al., 2008
miR125a	Invasion	Cortez et al., 2010
miR-128	Oncogenes, Stem cell renewal factor	Godlewski et al., 2008
miR-137	Differentiation	Silber et al., 2008
miR-146b-5p	EGFR, Migration, Invasion	Fowler et al., 2011; Xia et al., 2009
miR-153	Apoptosis	Xu et al., 2010; Xu et al., 2011
miR-181	Resistance	Slaby et al., 2010
miR-181a	Radiosensitivity	Chen et al., 2010
miR-181b	Proliferation	Conti et al., 2009
miR-195	Resistance	Ujifuku et al., 2010
miR-196	Prognosis	Guan et al., 2010
miR-221/222	P27(kip) survivin, radiosensitivity, PUMA	Wang et al., 2011; Zhang CZ et al., 2010; Zhang C et al., 2009; Lorimer, 2009; Zhang et al., 2009; Conti et al., 2009; Lukiw et al., 2009; Gillies & Lorimer, 2007
miR-326	Pyurvate kinase M2	Kefas et al., 2010
miR-328	ABCG2 expression, resistance	Li et al., 2010
miR-451	Tumor suppressor, proliferation, migration, resistance, metabolic stress	Nan et al,2010; Godlewski et al., 2010; Godlewski et al., 2010; Gal et al., 2008
miR-455-3p	Resistance	Ujifuku et al., 2010

Table 1. MicroRNA implicated in Glioblastoma Progression and Treatment

4.9 Implications of targeting the blood-brain barrier in developing novel approaches

Targeting drugs that cross the blood-brain barrier (BBB) to reach the extracellular/interstitial space (ECS) in brain post formidable challenges because the capillary endothelial cells are lined with intercellular tight junctions that restrict transfer of molecules from blood to the ECS (Lino & Merlo, 2009; Patel et al., 2009; Redzic, 2011). Moreover, the capillary endothelium on the brain side is completely surrounded or wrapped by astroglial end feet (Patel et al., 2009; Redzic, 2011). Several strategies have been proposed to deal with the restrictions of the BBB. Such strategies include: chemically modified delivery systems; biologically assisted delivery systems; disruption of the BBB; use of molecular Trojan horses such as peptidomimetic monoclonal antibodies; and particulate drug carrier systems (Juillerat-Jeanneret , 2008; Patel et al., 2009). Nevertheless, among these strategies, which are particularly suitable for delivering drugs to target glioblastomas remain to be definitively ascertained. Glioblastomas are cancer cells that exhibit diverse genotypic and phenotypic characteristics that allow them to adapt to their microenvironment so as to facilitate their proliferation and invasion into the surrounding normal brain tissue (see Lino & Merlo, 2009 and references therein). Consequently, further research is needed to combine a realistic assessment of their genotypic and phenotypic characteristics and how they adapt to their intracerebral niche along with selecting the appropriate strategy to target the desired efficacious chemotherapeutic agent to such gliomas. For example, on the one hand, around low-grade gliomas, the BBB is intact and usually restrictive to drug penetration; on the other hand, around high-grade, more malignant gliomas, the BBB becomes leaky as a result of the tumors actively secreting proteases and other factors that can actively degrade the tight junctions between the endothelial cells at their vicinity (Lino & Merlo, 2009). However, as the tumor grows aggressively, an increasing pressure in the ECS is being built up, ultimately leading to capillary and venous collapse. Consequently, any strategizing in optimizing the delivery of chemotherapeutic agents to the gliomas will have to consider the physiological and/or pathophysiological status of the capillaries that deliver oxygen and nutrients to the gliomas.

5. Conclusions

Several new approaches have been developed to treat glioblastomas during the last two decades. However, these approaches have not resulted in lowering the mortality and morbidity of patients suffering from this disease. The reason for this therapeutic inadequacy is that we are dealing with a tumor with highly malignant character and that the presence of the blood-brain barrier precludes easy access for drugs to target to the tumor. We have discussed the progress in understanding the aggressive phenotypic characteristics of glioblastomas and identified multiple drug targets (including key cell signaling and invasive processes) for treatment of this devastating disease. We have also emphasized the importance and the need to fully elucidate metabolic adaptive characteristics of glioblastoma employing the versatile new techniques involving nuclear magnetic resonance spectroscopy and imaging. Additionally, we have highlighted the use of new technologies whereby the restrictions of the blood-brain barrier to drug targeting can be circumvented. We included a brief review of some new roles of micro-RNAs in glioblastoma progression and treatment and showed their potential in mapping new strategies in treating glioblastomas. Ultimately, a successful strategy in treating glioblastomas leading to

improved patient outcome and survival necessarily involves a combination of drug targets based on a deeper appreciation of the metabolic adaptations of glioblastomas.

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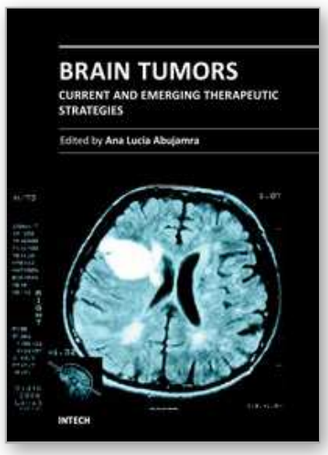

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