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Targeting Energy Metabolism to Overcome Therapeutic Resistance of Glioblastoma and Tumor-associated Edema

Biplab Dasgupta[1] • Yoshihisa Hirota[2,3] • Yuki Fujii[2,4] • Natsuki Osaka[5] • Doshun Ito[6] • David R. Plas[7] • Atsuo T. Sasaki[2,5,7,8]

[1]Division of Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [2]Division of Hematology and Oncology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [3]Department of Bioscience and Engineering, College of Systems Engineering and Science, Shibaura Institute of Technology, Fukasaku, Minuma-ku, Saitama, Japan; [4]Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka, Japan; [5]Institute for Advanced Biosciences, Keio University, Tsuruoka, Japan; [6]Structural Biology Research Center, Institute of Materials Structure Science, High Energy Accelerator Research Organization (KEK), Tsukuba, Ibaraki, Japan; [7]Department of Cancer Biology, University of Cincinnati College of Medicine, OH, USA; [8]Department of Neurosurgery, Brain Tumor Center at UC Gardner Neuroscience Institute, Cincinnati, OH, USA

Author for correspondence: Atsuo T. Sasaki, Division of Hematology and Oncology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH, USA. Email: atsuo.sasaki@uc.edu

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Abstract: Glioblastoma remains among the most lethal of human malignancies. The current standard of care prolongs life expectancy about 2 months on average compared to from radiation therapy alone, leading to a median patient survival of 14.6 months. Glioblastoma is heterogenous tumor at various levels, and intrinsically resistance to radiation and chemotherapy. These limits therapeutic

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options for both primary and recurrent tumors. Importantly, glioblastoma progression is often accompanied by cerebral edema, a significant cause of morbidity that influences the clinical course and prognosis of the disease. Immunosuppressive corticosteroids have been the primary treatment for glioblastoma-associated edema. However, the effect is temporary and accompanied by adverse effects due to the action of corticosteroids outside of the targeted area. Research over the past two decades has unveiled a significant role for metabolic reprogramming that confers a survival advantage during gliomagenesis and therapeutic resistance. This chapter introduces the recent discoveries of two energy metabolism pathways: AMP-activated kinase-mediated stress-resilient glioblastoma growth, and Guanosine-5'-triphosphate (GTP)- metabolic reprogramming that renders anabolic growth and radioresistance. We discuss the potential clinical utility of currently available medicine that could target these metabolic pathways to suppress malignant growth of glioblastoma and increase the efficacy of the current glioblastoma therapy.

Keywords: energy metabolism; edema; purine nucleotide metabolism; radioresistance; radiosensitivity

INTRODUCTION

Gliomas are the most common malignant primary tumors of the central nervous system (1). Glioblastoma (GBM) is the grade IV glioma based on the WHO classification (2), and constitute about 54% of all gliomas (1). For high-grade gliomas (*i.e.*, WHO grade III and IV), the 5-year survival rate is below 10%, even with aggressive treatment of surgical resection with adjuvant radiation and chemotherapy. Even low-grade glioma (WHO grade II) are ultimately lethal, with a median survival term of 6–8 years (3, 4). Currently, curative treatments are unavailable for glioma.

Radiotherapy is one of the primary treatment modalities (5), constituting a part of the current standard of care (6). However, glioblastomas are intrinsically resistant to radiotherapy (7–15) due to increased ROS resistance mediated by mechanisms not currently understood (13, 14, 16–18). Radiation therapy yields only marginal improvements in patient survival (19, 20), with a recurrence rate of nearly 80% despite use of high dose radiation (21, 22). The current standard of care treatment for glioblastoma includes maximal safe surgical resection followed by adjuvant radiotherapy plus DNA alkylating reagent temozolomide chemotherapy, which prolonged a median patient survival of 14.6 months, from that of 10. 6 months of radiotherapy alone (19, 20).

Most glioblastoma patients (>60%) suffer from glioblastoma-associated cerebral edema that represents a major cause of morbidity in glioblastoma. Patients with cerebral edema experience headaches, seizures, dysphagia, and cognitive and personality changes. The accumulation of fluids increases intracranial pressure, leading to ischemia, herniation, and ultimately death (23). Furthermore, glioblastoma-associated edema influences the clinical course and the prognosis of the disease (24, 25). Inflammation and neoangiogenesis, which destroy the integrity of the blood-brain barrier (BBB) causing fluid leakage, are two major causes

of glioblastoma-associated edema. Immunosuppressive corticosteroids have been the primary treatment for glioblastoma-associated edema since the 1960s. However, the effect is temporary and accompanied by adverse effects due to the systemic effects of corticosteroids (26–28). Importantly, recent studies show that corticosteroids may reduce survival in human glioblastoma patients (26–28) and murine glioblastoma model (29). Vascular endothelial growth factor (VEGF)-signaling inhibitor bevacizumab (Avastin) has an anti-edema effect; however, it does not extend patient survival (30–32) and causes adverse events, including hypertension, arterial and venous thrombosis, intracerebral hemorrhage, and slow wound healing (30, 33–35). Our recent studies about energy metabolism in GBM implicate the potential of repurposing existing drugs that could lead to the resensitization of glioblastoma patients to radiation therapy or/and suppress glioblastoma-associated edema while inhibiting tumor growth.

In the past decades, extensive research has uncovered genetic mutations (36–43), transcriptional changes (44–51), and reconfiguration of signaling pathways (49, 52–55) in glioblastoma pathogenesis. These studies reveal that glioma is highly heterogeneous, enabling multiple robust transcriptional, signaling, and metabolic programs that mediate apoptosis resistance of glioblastoma during tumorigenesis and confer therapeutic resistance. Importantly, even before the era of molecular biology, metabolic changes in glioma have been noted (55, 56). In the 1940s, a series of biochemical analyses conducted on human brain tumors, including glioma, revealed significant elevations of lipids in these tumors, particularly glioma (56, 57). More recent studies with advanced molecular methods and high-sensitivity mass spectrometry-based analytical methods have clarified a mechanistic basis of the metabolic changes to increase lipid synthesis and accumulation of lipid droplets in glioma and glioma stem cells, contributing to the malignant growth of gliomas (58–61). The changes in nucleotide metabolism in glioma was denoted in the early 1950s (62), which is in part confirmed by enzymatic analysis that shows dramatic suppression of salvage GTP biosynthetic enzymes in glioma in 1994 (63), further followed by recent molecular studies (64, 65). These metabolic changes provide the building blocks for major cellular constituents—proteins, lipids, and nucleotides—to match the high metabolic demand of rapidly growing glioma cells (66). Notably, more recent studies, including ours, have shown critical metabolic pathways that induce coordinated anabolic growth through multiple mechanisms (67–70).

This chapter introduces two energy metabolism-related signaling pathways—AMP-activated kinase (AMPK) and guanosine-5'-triphosphate (GTP) metabolism—that are activated in glioma. Then, we discuss the possible therapeutic benefits of targeting these energy metabolisms to suppress glioma progression and sensitize glioma for the current therapeutics in particular radiotherapy.

EMERGING ROLES OF ENERGY METABOLISM IN GLIOBLASTOMA AND THERAPEUTIC TARGETING

In part, glioblastoma malignancy stems from its increased resistance to stress conditions during gliomagenesis, which is positively associated with therapeutic

resistance, including radiation therapy (7–15). Until recently, whether and how cellular metabolism is integrated into the process of glioma formation, progression and stress resilient growth is understudied. This section introduces emerging roles of energy metabolism in gliomagenesis and its potential clinical utility as a new therapeutic target for glioblastoma.

ATP energy sensor, AMPK, is critical to overcoming stresses during gliomagenesis

Stress is central to tumor evolution (71). The success of tumor cells in the hostile tumor milieu depends on how well tumor cells activate stress management pathways. Metabolic stress in solid tumors like glioblastoma poses a formidable challenge for tumor cell survival. These stresses include nutrient, hypoxic, pH, and oxidative stress in addition to therapy-induced xenobiotic stress (71–73). Metabolic stress is often caused by energy stress, which reduces the cellular ATP to AMP ratio and activates the energy sensor AMPK (74, 75) (Figure 1). Once activated, AMPK augments energy-generating reactions such as glycolysis and mitochondrial oxidative phosphorylation of glucose and fatty acids (74, 75).

Because AMPK is part of the liver kinase B1 (LKB1) tumor suppressor pathway and turns off major biosynthetic reactions such as lipid and protein synthesis—processes that are key to tumor cell growth and proliferation—it was long

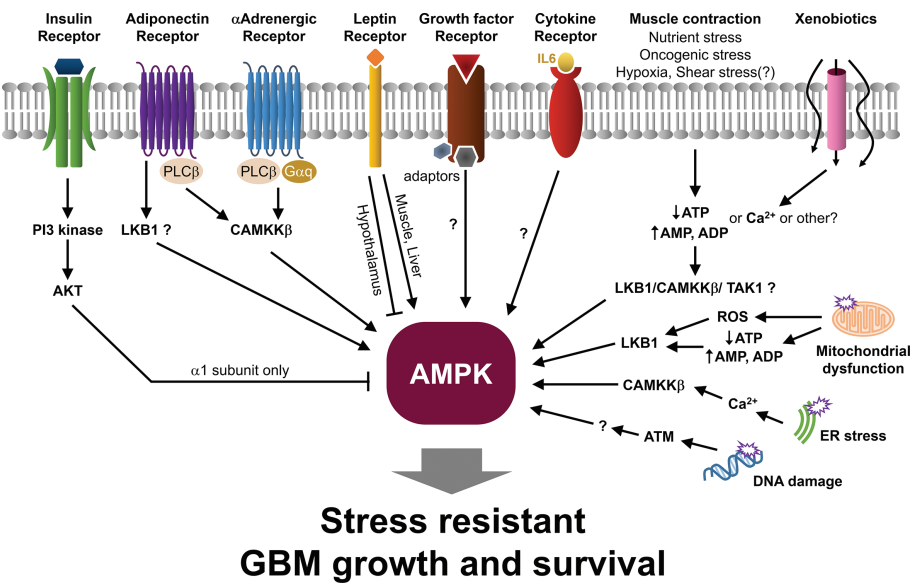

Figure 1. Activation of AMPK pathway has glioblastoma cells to be high stress resistant. AMPK receives many intra- and extra-cellular signals as a part of LKB1, CAMKKb, and other pathways. Activated AMPK leads to high stress resistance of GBM cells and supports their growth and survival.

believed that AMPK had a net suppressive role in tumorigenesis, including glioblastoma (76). However, AMPK-deficient transformed cells under tumor-like hypoxic conditions have a growth disadvantage *in vivo* (77). Taking an orthogonal approach, we determined that AMPK activity is abundant in all high-grade gliomas regardless of the genetic background of the tumors (78, 79). We showed that through transcriptional control of glioblastoma bioenergetics AMPK is required for optimal growth and survival of glioblastoma (79). Studies from other laboratories also concluded a role for AMPK in glioma pathogenesis. In an N-ethyl-N-nitrosourea-induced rat model of brain tumors, high AMPK activity was reported from the early hyperplastic lesions to the fully formed tumors (80). In a mouse model of astrocytoma driven by mutant *HRas* and *Pten* deletion, AMPK was necessary to maintain astrocytoma proliferation and survival (81) and lipoprotein internalization (82). The inhibitory role of AMPK on major biosynthetic processes that are required for cell growth and division appears paradoxical to the presence of high levels of active AMPK in glioblastoma and other solid tumors. However, as the tumor grows in volume, a plethora of tumor-specific stress builds up. This includes oncogenic stress, nutrient and oxygen stress due to fluctuating nutrients and oxygen levels and malformed neovasculature, and pH stress caused by the harsh acidic environment. These stresses reprogram tumor metabolism that allows tumor cells to survive and thrive in this stressful tumor microenvironment. Although the mechanisms are not fully clear, active AMPK may support this altered tumor metabolism and tumor cell survival (74).

A potential of AMPK targeting to enhance the efficacy of radiation therapy

One of the important consequences of AMPK activation is the upregulation of autophagy. Importantly, the enhanced autophagy contributes to radioresistance in glioblastoma and many other tumors (83–86). *A priori*, AMPK activation constitutes a key element of glioblastoma radioresistance (87, 88). Up to now, agents that indirectly activate AMPK were used to suppress tumor cell growth, including glioma growth (89–91). Notable agents include the antidiabetic biguanide drugs (metformin and phenformin) and the *de novo* purine synthesis pathway metabolite AICAR. Biguanides inhibit mitochondrial complex I and cause energy stress, while AICAR metabolizes to ZMP, which mimics AMP—each process activating AMPK (92, 93). Importantly, metformin has been shown to increase radiosensitivity (94–96). Although this may appear paradoxical, studies from our laboratory have shown that the anti-glioma effects of AICAR and biguanides are not only AMPK-independent but, in fact, AMPK-silenced glioma cells lose metabolic plasticity and become more vulnerable to the cytotoxic effects of AICAR and biguanides (78). This loss of metabolic plasticity of AMPK pathway deficient cells is likely conserved across other tumor types since LKB1 null lung cancer cells are also hypersensitive to biguanides (97). Together, results from preclinical and clinical studies illuminate a unique opportunity to use biguanides in clinical trials in combination with AMPK inhibitors, which are currently under development in our laboratory. The expectation is that this combination will likely synergize to overcome the radioresistance of glioblastoma.

GTP METABOLIC REPROGRAMMING PROMOTES GLIOBLASTOMA MALIGNANCY

ATP and GTP are involved in many cellular functions, including DNA and RNA building blocks, energy sources, enzymatic cofactors in metabolic pathways, and components of signal transduction. There are two pathways to produce GTP. *De novo* GTP synthesis involves a multi-step, high nutrient and energy-consuming pathway. Glucose is converted to GTP through 19 enzymatic steps that use a glycine molecule, an aspartate molecule, 3 glutamines, 2 N^{10}-formyl-THF, and 10 ATP. In contrast, the salvage pathway is an energy-efficient process in which a nucleoside (inosine, guanosine) and a nucleobase (hypoxanthine, guanine) are recycled to produce a GTP (98, 99) (Figure 2). As a result, the use of the salvage pathway is heavily favored in adult tissues, particularly in the adult brain (100–102). Importantly, many tumors increase GTP levels more than the other ribonucleotides, including glioblastoma (65, 103). However, how and why tumors alter GTP metabolism for their malignant growth has not previously been explored.

To that end, we have discovered a lipid kinase PI5P4Kβ as an intracellular GTP sensor regulating the metabolism and the tumorigenic process in accordance with cellular GTP energy levels (104, 105). Also, a recent publication of ours showed that GTP biosynthesis is significantly upregulated in glioblastoma by IMP dehydrogenase isozyme-2 (IMPDH2), which promotes enhanced ribosome biogenesis and tRNA synthesis, cooperating malignant glioblastoma growth *in vitro* and *in vivo* while normal brain cells operate without this GTP biosynthetic pathway (65). IMPDH2 mRNA expression is not significantly correlated with IMPDH2 protein levels, suggesting posttranscriptional regulation and therefore the importance of immunohistochemical analysis to evaluate the IMPDH2 levels. Importantly, increased IMPHD2 is correlated with poor survival of glioma patients regardless of IDH mutational status (65). Mechanistically, IMPDH2 upregulation promotes *de novo* GTP biosynthesis for ribosome biogenesis and tRNA synthesis, leading to nucleolar enlargement and malignant growth of glioblastoma (Figure 3). Inhibition of IMPDH2 decreases nucleolar size and significantly suppresses glioblastoma growth in *vitro* and *vivo* (65). The significance of IMPDH2 in glioblastoma and multiple cancers is also supported by other studies (68, 99, 106). Together, these studies illuminate the potential of targeting IMPDH-dependent GTP synthesis as a treatment for glioma. Importantly, there are FDA-approved inhibitors for IMPDH, including MPA and MMF (Figure 3) (106).

Targeting the GTP metabolic reprogramming to increase the efficacy of radiation therapy

Nucleotides are essential factors for genome stability and DNA repair (107–110). Importantly, studies of radioresistant bacteria, *Micrococcus luteus*, suggest that the GTP-metabolism is associated with radioresistance (111, 112). In cancer cells, IMPDH inhibition causes DNA lesions (113) and suppresses DNA damage-repair induced by radiation (114, 115). Radioresistant glioblastoma cell lines and glioblastoma-stem-like cells are capable of increasing guanylate levels in response to radiation (116). MPA/MMF treatment prevents this, leading to decreased DNA

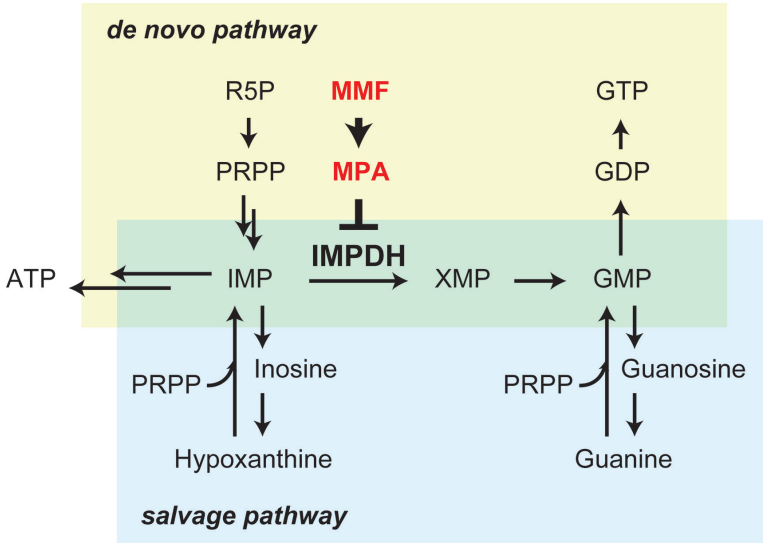

Figure 2. Two types of GTP synthesis pathways. GTP synthesis is controlled by two pathways. A sugar, phosphoribosyl diphosphate (PRPP), is made by ribose-5-phosphate (R5P) involved in pentose phosphate pathway. In *de novo* pathway, IMP is generated from PRPP through high nutrient and energy consuming reactions. On the other hand, salvage pathway produces a new IMP or GMP by directly connecting a sugar (PRPP) and a nucleobase (hypoxanthine or guanine). These nucleobases come from recycled IMP or GMP metabolites (inosine or guanosine). This economical pathway is favored in adult tissues. IMP dehydrogenase (IMPDH) oxidizes IMP to XMP. IMPDH is involved in the first step of guanine nucleotide synthesis and plays important roles in proliferation, cellular homeostasis, and also tumors facilitation including GBM. IMPDH activity is strongly inhibited by mycophenolate mofetil (MMF), which is a precursor of mycophenolic acid (MPA) and uses as prodrug of immunosuppressant. ATP, adenosine triphosphate; GDP, guanosine diphosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; IMP, inosine monophosphate; IMPDH, IMP dehydrogenase; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PRPP, phosphoribosyl diphosphate; R5P, ribose-5-phosphate; XMP, xanthine monophosphate.

repair and clonogenic glioblastoma growth, thereby extending survival in an orthotopic PDX-glioblastoma model (116). In osteosarcoma U2OS cells, IMPDH2 overexpression increases radioresistance, while IMPDH2 knock-down increases radiosensitivity (117). These results suggest the previously unrecognized role of IMPDH2 in radioresistance (Figure 3). Importantly, Phase 0/1 Trial (NCT04477200) looking at the effects of MMF with radiation has been initiated to define the maximum tolerated dose of MMF when administered with radiation, in patients with recurrent glioblastoma or recurrent gliosarcoma. As of December 2020, our multidisciplinary group at the University of Cincinnati is in the preparation of a new MMF trial for glioblastoma treatment from a different angle, which is to treat GBM-associated edema by MMF. Collectively, repurposing IMPDH inhibitors has an important potential for new glioblastoma therapeutics and should be further studied to develop more effective, optimally designed therapeutics for clinical utilization to overcome radiation resistance and complications associated with glioblastoma.

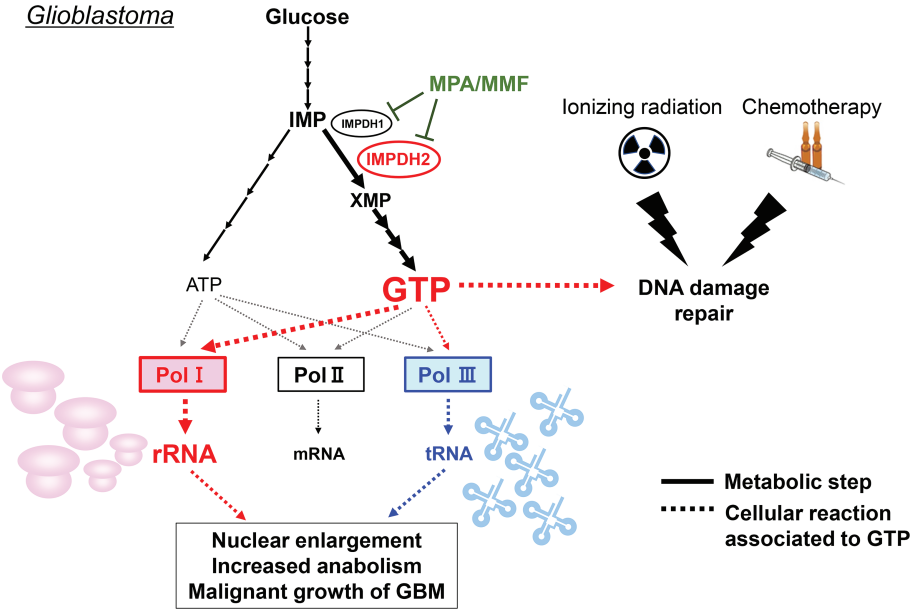

Figure 3. Upregulation of *de novo* GTP biosynthesis by IMPDH2 generates aberrant phenotype of Glioblastoma. In Glioblastoma (GBM), *de novo* GTP biosynthesis is upregulated by IMPDH2. Increasing GTP levels promotes rRNA and tRNA synthesis through transcription by RNA polymerase I (Pol I) and RNA polymerase III (Pol III) respectively. Upregulation of r/tRNA synthesis cause nuclear enlargement, increased anabolism, and malignant growth. Moreover, elevated GTP promotes DNA damage repair for radioresistance in GBM. MPA and MMF, the inhibitor for IMPDH, block both r/tRNA synthesis. Moreover, decrease in GTP levels by MPA and MMF indirectly inhibits GTP-associated DNA damage repair. Solid line indicates the metabolic step and dotted line indicates the cellular reactions associated to GTP.

A possible utility of the immunosuppressive effect of MMF to ameliorate glioblastoma-associated edema

Since MMF has been used as a potent immunosuppressor for tissue transplanted patients and autoimmune disease, a potential caveat of MMF or any IMPDH inhibitor is that it may limit the use of an upfront glioblastoma setting. However, we propose that MMF's use may be beneficial in some situations, particularly glioblastoma-associated edema treatment, based on the following evidence:

(i) *MMF suppresses inflammation and stroke-associated edema:* MMF is used globally for organ transplanted patients and possesses greater potency for the IMPDH2 isozyme (118). Importantly, MMF inhibits activation of microglia and astrocytes (119) and monocyte recruitment to endothelial cells (120, 121). In the LPS-stimulated BALB/c mouse neuroinflammation model, MMF treatment suppressed the expression of pro-inflammatory proteins (for example, iNOS, COX-2, TNFα, IL-1β, IL-6) (122). Furthermore, MMF treatment suppressed cerebral edema in stroke-prone spontaneous hypertensive rats (SHR-A3) (123).

(ii) *MMF suppresses neoangiogenesis:* Several reports indicate a critical link between IMPDH2 and neoangiogenesis. Two studies using zebrafish embryos show that IMPDH2, but not IMPDH1, is highly expressed at the sites of new blood vessels, and MPA treatment suppresses angiogenesis (124, 125). MPA treatment suppressed angiogenesis of human endothelial cells (126, 127). Oral administration of MMF significantly suppressed *in vivo* angiogenesis induced by melanoma (128), pancreatic cancer (129, 130) and U87MG glioma (127). Importantly, our preliminary studies using hCMEC/D3 cells, widely used as BBB models (131–137), show that MPA treatment does not disrupt the integrity of BBB.

Thus, MMF treatment has a high potential to suppress neoangiogenesis while maintaining BBB integrity. Currently, our multidisciplinary group at the University of Cincinnati is actively pursuing research to clarify the utility of MMF for glioblastoma edema treatment.

CONCLUSION

Despite the advances in general cancer treatment, glioblastoma remains among the most lethal of human malignancies. Even with aggressive multimodal radiation and chemotherapy after surgery, radiation therapy yielded marginal improvements in patient survival (19, 20) due to the radioresistant nature of glioblastoma. It is crucial to develop more effective therapeutics to improve the prognosis of the average patient with a glioblastoma and identify glioblastoma vulnerabilities for new potential targets and test the setting in clinically relevant glioblastoma animal models. In this chapter, we have introduced new potential targets for glioblastoma therapy, which are expected to suppress glioblastoma regardless of mutational status and increase the efficacy of the current therapeutic regimen when combined. For the next stage, it is crucial to further investigate the drugs targeting AMPK and IMPDH on the survival, therapeutic resistance, and edema formation of immunocompetent glioblastoma mouse models, and assess pharmacodynamics and identify PD markers. It is also imperative to study the combinations of these drugs with radiation therapy, including upfront proton beam therapy as introduced in the following chapter.

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