Targeting Metabolic Vulnerabilities in Glioblastoma: Disrupting Glycolysis, Glutaminolysis, and Mitochondrial Function

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Introduction

Glioblastoma (GBM) exhibits metabolic reprogramming characterized by preferential reliance on aerobic glycolysis (Warburg effect), enhanced glutaminolysis, and altered mitochondrial function. This metabolic inflexibility increases dependence on glucose and glutamine, creating potential therapeutic vulnerabilities. Targeting these pathways has emerged as a strategy to disrupt sustained tumor growth and survival.

Objective

To summarize current metabolic targeting strategies in GBM, including dietary modification, glycolysis inhibition, glutaminolysis inhibition, and mitochondrial-directed therapies.

Methods

Narrative review of **152 peer-reviewed publications** (2000–2025)
Databases: PubMed, Embase, Web of Science
Inclusion: Preclinical, translational, and clinical GBM studies
Exclusion: Case reports, non-primary brain tumors
Focus: ketogenic diet (KD), glycolytic inhibitors (PKM2, PDK/DCA), glutaminase inhibitors (GLS, GDH), and mitochondrial targets (VDAC1), including effects on tumor metabolism and immune microenvironment.

Results

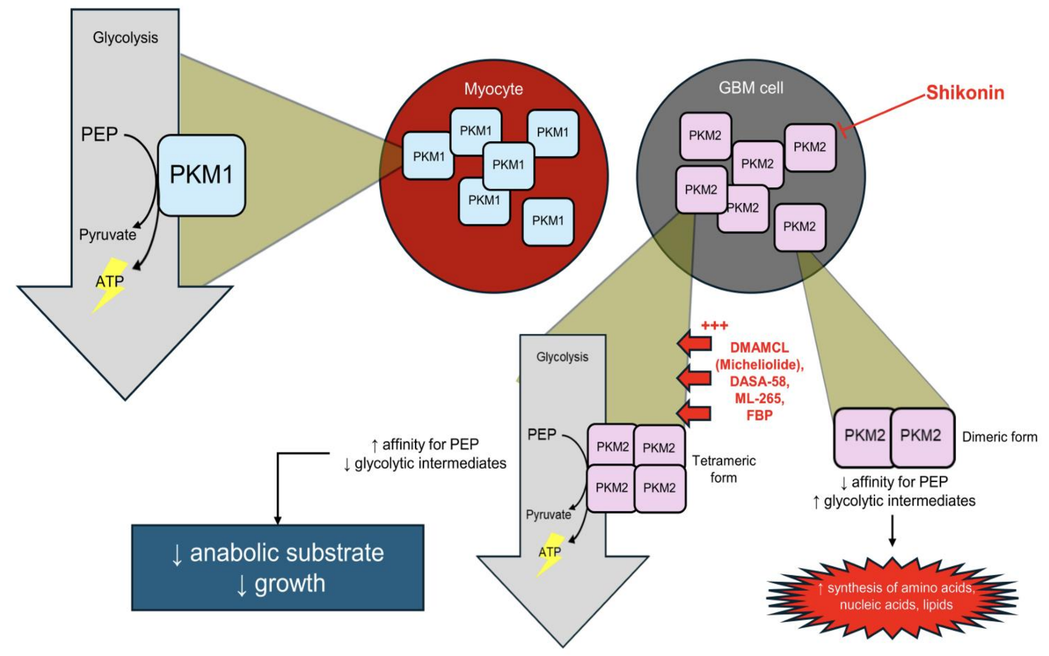

Figure 1

PKM2-targeted strategies in GBM: inhibition or tetramer activation to disrupt tumor metabolism.

Target Pathway	Strategy / Agent	Mechanism of Action	Preclinical Findings
Glucose Restriction	Ketogenic Diet (KD)	Induces ketosis (↑β-hydroxybutyrate), ↓ glucose availability, ↑ oxidative stress, immune modulation	↑ sensitivity to radiation/chemotherapy; immune modulation; mixed macrophage effects
Glycolysis (PDK)	Dichloroacetate (DCA)	Inhibits PDK → Reactivates PDH → Forces OXPHOS → Reverses Warburg effect	↑ mitochondrial membrane potential; ↑ apoptosis; ↓ glycolysis; tumor regression in models
Glycolysis (PKM2 inhibition)	Shikonin	Inhibits PKM2 phosphorylation (Tyr105) → ↓ aerobic glycolysis	↓ glucose consumption; ↓ lactate production; ↓ tumor growth in models
Glycolysis (PKM2 activation)	DMAMCL, DASA-58, ML265	Force PKM2 tetramerization → Maximal glycolytic flux → ↓ anabolic intermediates	↓ proliferation; ↓ glycolytic intermediates; tumor suppression in xenografts
Glutaminolysis (GLS inhibition)	CB-839 (Telaglenastat)	Allosteric GLS inhibitor → ↓ α-KG, ↓ NADPH, ↓ nucleotide synthesis	Strong dose-dependent anti-proliferative effects in GBM cell lines
Glutaminolysis (GLS inhibition)	BPTES, C968	Stabilize inactive GLS (GAC isoform)	↓ α-KG; ↓ GBM proliferation (variable findings for C968)
Glutaminolysis (GDH inhibition)	EGCG, R162	Inhibit GDH → ↓ α-KG generation	↓ proliferation and migration in GBM xenografts
Mitochondrial Targeting	VDAC1 inhibitors (Tf-D-LP4, D-DN-Ter-Antp), itraconazole	Disrupt metabolite flux; induce cytochrome c release; ↓ ATP	↓ ATP (up to 80%); ↑ apoptosis; 45–60% tumor reduction in xenografts

Conclusions

Metabolic targeting strategies exploiting glycolysis, glutaminolysis, and mitochondrial dysfunction provide compelling preclinical evidence for therapeutic vulnerability in GBM. Agents such as DCA and CB-839 demonstrate strong mechanistic rationale for clinical translation. However, well-powered clinical trials are necessary to determine whether these approaches improve survival outcomes in GBM patients.

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