Genetic Drivers of Energetic Reprogramming and Immune Escape in Glioblastoma

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Introduction

Glioblastoma (GBM) is a highly aggressive primary CNS malignancy characterized by complex genetic and molecular aberrations. Despite advances in surgery, radiation, and chemotherapy, prognosis remains poor. A defining feature of GBM pathogenesis is **profound metabolic reprogramming**, most notably the **Warburg effect**, or preferential reliance on aerobic glycolysis. This metabolic shift, driven by oncogenic signaling and the tumor microenvironment (TME), underlies tumor adaptability, survival, and immune evasion.

Objective

To synthesize key **metabolic pathways**, **genetic drivers**, and **tumor–immune interactions** that define GBM aggressiveness and identify actionable metabolic vulnerabilities.

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: metabolic pathways, IDH status, EGFR/PTEN signaling, HIF-1α, lactate transport (MCT1/4), glutaminolysis (GLS), lipid metabolism, immune modulation.

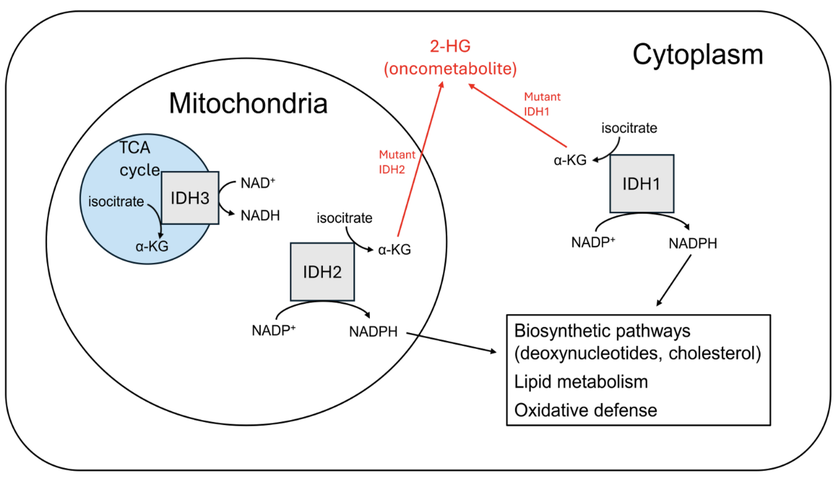

Figure 1
IDH isoforms differ by cofactor use, localization, and metabolic function.

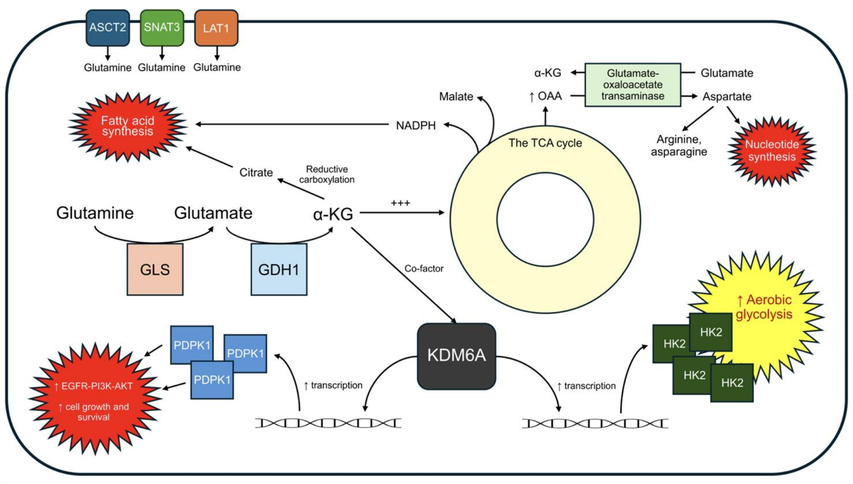

Figure 2
Glutaminolysis supports GBM growth through NADPH production, anaplerosis, and signal amplification.

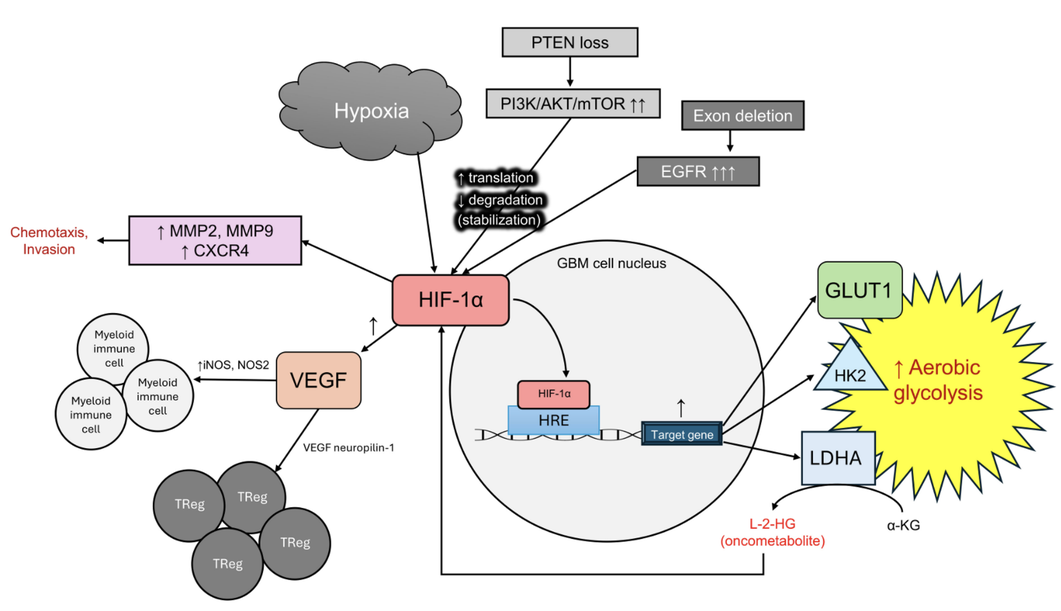

Figure 3
HIF-1α as a regulator of metabolic reprogramming, invasion, and immune modulation in GBM.

Results

Category	Key Findings	Functional Consequence
IDH Mutations	Mutant IDH1/2 converts α-KG → 2-HG	Inhibits α-KG–dependent enzymes → Pseudohypoxia → Stabilization of HIF-1α and VEGF
IDH Wild-Type GBM	EGFR amplification; PTEN loss	Activates PI3K/Akt/mTOR → Sustained HIF-1α signaling and anabolic growth
HIF-1α Activation	Upregulates GLUT1, HK2, LDHA	Accelerated glycolysis (Warburg effect) and increased lactate production
Lactate Shuttle	MCT4 (export, tumor core); MCT1 (import, periphery)	Metabolic flexibility between glycolysis and OXPHOS across tumor regions
Immune Modulation	Lactate stabilizes HIF-1α in macrophages; increases ARG1, VEGF	Promotes M2 macrophage polarization and immunosuppressive TME
Treg Activation	Lactate increases CTLA-4 expression	Enhances regulatory T-cell suppression
CD8+ T-cell Dysfunction	Lactate–proton accumulation disrupts MCT1 gradients	Impairs cytotoxic T-cell proliferation and effector function
Glutaminolysis	Increased GLS and GDH1 activity	Supports anaplerosis, NADPH production, and amplifies PI3K signaling
Lipid & Cholesterol Synthesis	Upregulation of FASN, ACC, SREBP2	Sustains membrane synthesis and tumor proliferation
OXPHOS-Dominant Subtype	Elevated mitochondrial metabolism	Distinct metabolic phenotype associated with improved survival

Conclusions

GBM survival depends on a **flexible metabolic framework** integrating oncogenic signaling, enhanced anabolism (glycolysis, glutaminolysis, lipogenesis), and TME-driven immune modulation.

Key vulnerabilities include:
- Constitutive **HIF-1α activity**
- Lactate transport and signaling
- Targetable metabolic enzymes (e.g., GLS, ACC)

Addressing metabolic heterogeneity represents a promising therapeutic strategy in GBM.

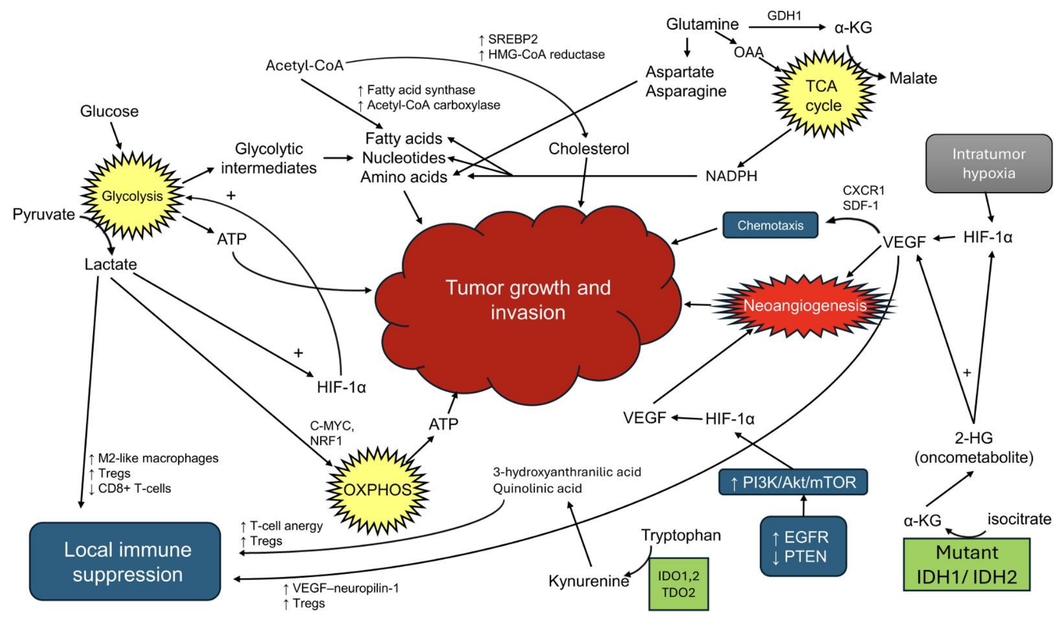

Figure 4
Overview of key molecular and metabolic pathways in GBM.

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