Hypoxia-Targeted Therapeutic Strategies in Glioblastoma: A Narrative Review of Emerging Clinical and Preclinical Evidence

Jawad A Saad, BS; James Chung, BS; Ahmad Kafri, BS; Julien Rossignol, PhD; Maxwell Verbrugge, MD; Jesse Bakke, PhD
Central Michigan University College of Medicine

CENTRAL MICHIGAN UNIVERSITY

Introduction

Glioblastoma multiforme (GBM) is the most aggressive primary brain malignancy in adults, characterized by rapid proliferation, diffuse invasion, and resistance to standard therapy (surgical resection + radiotherapy + temozolomide).

A defining biological feature of GBM is **metabolic reprogramming**, which drives:

- Chronic intratumoral hypoxia
- Stabilization of **HIF-1α / HIF-2α**
- Upregulation of angiogenesis (VEGF), glycolysis (GLUT1, HK2, LDHA), invasion (MMP2/9)
- Promotion of stemness and therapeutic resistance

Hypoxia is not merely a byproduct of tumor growth but is a **central driver of malignant progression and treatment failure**.

Objective

To evaluate emerging hypoxia-directed strategies that:

1. Reverse tumor hypoxia
2. Exploit hypoxic tumor niches
3. Inhibit HIF-mediated transcriptional signaling
4. Enhance radiosensitivity and chemosensitivity

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
Focused thematic grouping on:

- Hypoxia-Activated Prodrugs (HAP)
- Hyperbaric Oxygen Therapy (HBOT)
- Oxygen Transport Agents (OTA)
- HIF inhibitors & small-molecule therapies

Discussion

Persistent tumor hypoxia drives HIF-mediated resistance in GBM despite maximal resection and chemoradiation.

Therapeutic strategies target hypoxia by:

- Exploiting low-oxygen conditions (HAPs)
- Increasing tumor oxygenation (HBOT, OTAs)
- Inhibiting HIF-driven metabolic signaling

Early-phase studies demonstrate acceptable safety and signals of improved response and survival in select cohorts.

Key limitations include tumor heterogeneity, variable hypoxic burden, and restricted BBB penetration.

These approaches are best viewed as **microenvironment-directed adjuncts** to standard therapy.

Conclusions

Targeting hypoxia-driven metabolic reprogramming represents a critical frontier in GBM therapy.

Combination strategies incorporating:

- Hypoxia-activated prodrugs
- Oxygen-enhancing interventions
- Direct HIF inhibition
- BBB-permeable small molecules

demonstrate encouraging safety and preliminary efficacy.

However, large-scale randomized trials and precision biomarker-driven approaches are required before integration into standard-of-care protocols.

Results Summary Table: Hypoxia-Directed Therapies in GBM

Therapeutic Category	Agent(s)	Target/Pathway	Key Clinical or Preclinical Outcomes	Mechanistic Impact in GBM
Hypoxia-Activated Prodrug (HAP)	Evofosfamide + Bevacizumab	Hypoxic tumor core	ORR: 17.4%; Disease control: 60.9%; Decreased hypoxic volume correlated with improved OS & PFS	Hypoxia-triggered Br-IPM release causing DNA crosslinking; Imaging biomarkers (FMISO PET, DSC-MRI) predictive
Hyperbaric Oxygen Therapy (HBOT)	HBOT + RT + TMZ	Tumor hypoxia / HIF axis	Median OS up to 22.1 months; Recurrent HGG OS: 10.7 months	Reduced HIF-1α/HIF-2α; Decreased ABCG2; Increased ROS-mediated radiosensitization
Oxygen Transport Agent (OTA)	Trans-sodium crocetinate (TSC) + RT/TMZ	Oxygen diffusion	36% 2-year survival (vs ~27% historical controls)	Enhanced oxygen diffusion through plasma restructuring
Microtubule / HIF Inhibitor	Noscapine	HIF-1α, VEGF	78% tumor volume reduction (murine); Synergistic with TMZ	Inhibits HIF-1α nuclear accumulation; Induces mitotic arrest
SRC Kinase Inhibitors	Si306, Pro-Si306	Migration/invasion signaling	Preclinical invasion suppression	FAK inhibition; Potential P-gp modulation
PI3K/Akt/mTOR Inhibitors	Celastrol, Isolinderalactone, Metformin	Hypoxia adaptation pathway	Reversal of chemoresistance (preclinical)	Suppresses angiogenesis and HIF-mediated signaling
TGF-β Pathway Inhibitors	Galunisertib, Disulfiram	Mesenchymal transition	Sensitization of resistant GBM (preclinical)	TGF-β receptor inhibition
Integrin Inhibitors	Cilengitide	αvβ3 / αvβ5	Tumor regression in xenografts	Disrupts EGFRvIII/integrin complex; Anti-angiogenic
Mitochondrial Metabolism Modulators	Atovaquone, Doramectin, Ivermectin	Tumor bioenergetics	Reduced viability (preclinical)	STAT3 inhibition; Increased oxidative stress; Mitochondrial dysfunction

Contact

Jawad A. Saad
Central Michigan University College of Medicine
Saad1ja@cmich.edu
LinkedIn: Scan QR Code

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