

ABSTRACT

Glioblastoma (GBM) uses metabolic plasticity to survive hypoxia, nutrient deprivation and genotoxic stress. This review examines how PKM2, ENO1 and GAPDH acquire non-canonical functions beyond glycolysis that support tumour adaptation. PKM2 promotes stress-responsive transcription, ENO1 drives proliferative and immune-evasive signalling, and GAPDH can regulate either survival or apoptosis depending on cellular stress. Integrating these functions reveals a coordinated stress-adaptation network and highlights potential therapeutic strategies that target these functions alongside existing treatment.

INTRODUCTION

- GBM has a harsh tumour microenvironment shaped by hypoxia, nutrient shortage, oxidative stress and DNA damage. These pressures drive metabolic reprogramming, including increased reliance on glycolysis through the Warburg effect.
- PKM2, ENO1 and GAPDH can move beyond their canonical glycolytic roles under stress, acquiring functions in transcription, signalling, immune regulation and apoptosis.
- GBM remains highly treatment-resistant, with a median survival of roughly 15 months and <5% of patients surviving beyond 5 years.

KNOWLEDGE GAP

While individual enzymes have been extensively studied, their collective contribution is a gap I have observed. This review synthesizes these functions as a coordinated stress-response system.

REVIEW OBJECTIVE

To synthesis the non canonical roles of PKM2, ENO1 and GAPDH and evaluate their integrated contribution to GBM progression and therapeutic poitential.

METHODS

Databases: PubMed and Google Scholar

Search terms: PKM2, ENO1, GAPDH, glioblastoma, non canonical functions, metabolic reprogramming, hypoxia, immune evasion, apoptosis, therapy resistance

Time frame: Last 12 years, along with foundational studies.

Selection process: Title/abstract screening, full text review, reference list review.

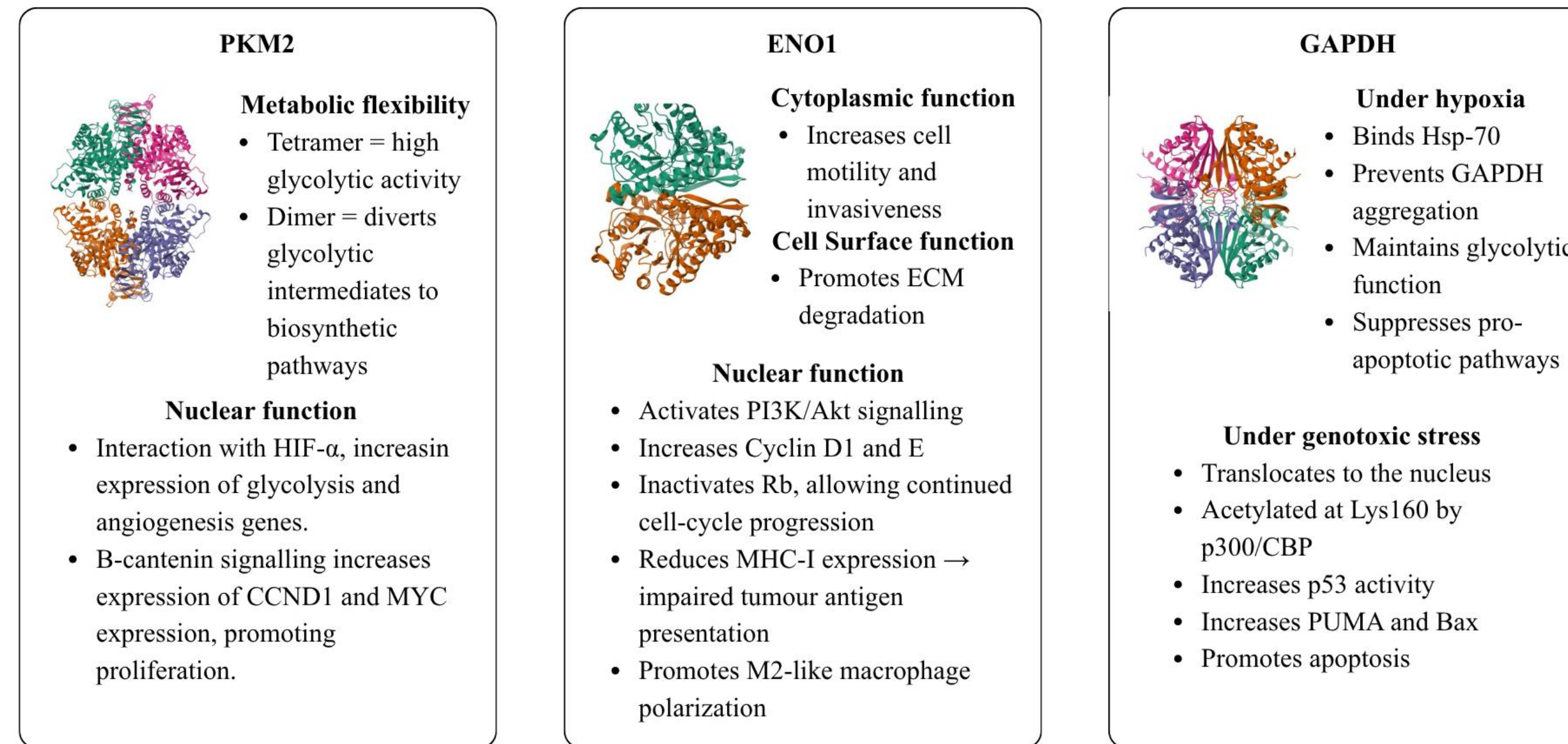
Synthesis: Evidence was integrated across molecular, cellular and therapeutic studies to examine how PKM2, ENO1 and GAPDH contribute collectively to stress adaptation.

RESULTS – AN INTEGRATED MODEL OF GBM STRESS ADAPTATION

1. Cellular stress in GBM microenvironment drives metabolic reprogramming

Hypoxia Nutrient Deprivation Oxidative Stress DNA damage Inflammatory signals

2. PKM2, ENO1 and GAPDH perform distiinct but complementary functions



3. Convergent outcomes result in GBM progression

Proliferation Angiogenesis Immune evasion Invasion Therapy resistance

Figure 1: Integrated Model Summarising how PKM2, ENO1 and GAPDH contribute to GBM stress adaptation through non canonical functions.

DISCUSSION

Current therapeutic strategies:

- PKM2, ENO1 and GAPDH are essential metabolic enzymes as well as drivers of tumour-promoting functions.
- Broad inhibition can disrupt glycolysis, ATP production and biosynthetic metabolism in normal cells.
- Current strategies show that targeting these enzymes can weaken GBM cells, but do not fully separate metabolic activity from non-canonical functions.

Therapeutic direction:

- PKM2: isoform-selective PROTACs could potentially target PKM2 while sparing PKM1.
- ENO1 and GAPDH: CRISPRi could reduce tumour-associated overexpression without completely eliminating enzyme activity.
- These approaches remain theoretical in GBM. BBB (Blood Brain Barrier) penetration, tumour-specific delivery, off-target effects and metabolic rewiring remain unresolved barriers.

RESULTS – THERAPEUTIC STRATEGIES

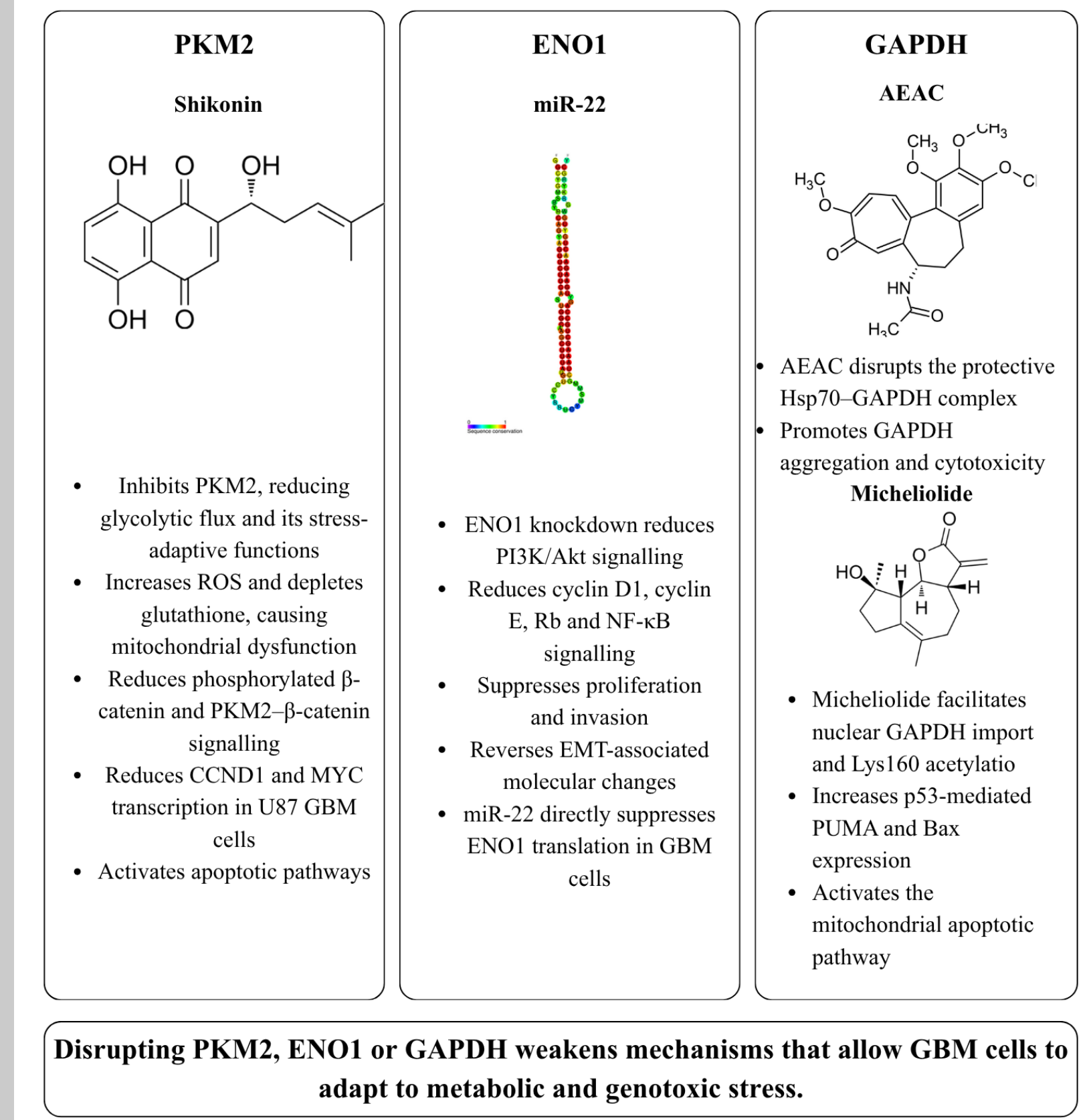


Figure 2: Experimental Targeting of PKM2, ENO1, and GAPDH in Glioblastoma

CONCLUSION

- PKM2, ENO1 and GAPDH collectively extend beyond glycolysis to help GBM respond to metabolic and genotoxic stress.
- Their functions are context- and location-dependent, linking metabolic reprogramming with proliferation, immune evasion, invasion and survival.
- The key contribution of this review is the integration of these enzymes into a coordinated stress-adaptation network, rather than treating their moonlighting functions independently.
- Future therapeutic strategies should aim to weaken tumour-specific adaptive functions while preserving essential metabolism, potentially sensitising GBM to existing chemotherapy and radiotherapy.

REFERENCES

- Baillleul, J., & Vlashi, E. (2023). Glioblastomas: hijacking metabolism to build a flexible shield for therapy resistance. *Antioxidants and Redox Signaling*, 39(13–15), 957–979. <https://doi.org/10.1089/ars.2022.0088>
- Luo, W., & Semenza, G. L. (2012). Emerging roles of PKM2 in cell metabolism and cancer progression. *Trends in Endocrinology and Metabolism*, 23(11), 560–566. <https://doi.org/10.1016/j.tem.2012.06.010>
- Trejo-Solis, C., Silva-Adaya, D., Serrano-García, N., Magaña-Maldonado, R., Jimenez-Farfán, D., Ferreira-Guerrero, E., Cruz-Salgado, A., & Castillo-Rodriguez, R. A. (2023). Role of Glycolytic and Glutamine Metabolism Reprogramming on the Proliferation, Invasion, and Apoptosis Resistance through Modulation of Signaling Pathways in Glioblastoma. *International Journal of Molecular Sciences*, 24(24), 17633. <https://doi.org/10.3390/ijms242417633>