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Research paper

# Hyperglycemia as driver of glioblastoma progression: Insights from Mendelian randomization and single-cell transcriptomics

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## Highlights

- Hyperglycemia is genetically associated with an increased risk of glioblastoma.
- Hyperglycemia promotes glioblastoma stem cell expansion and immunosuppressive macrophage polarization.

- GBM-related pathways are significantly upregulated in the brain tissue of type 2 diabetes patients.


## Abstract

### Background

Hyperglycemia and diabetes may influence GBM progression by altering tumor metabolism and the tumor microenvironment. However, the causal relationship between blood glucose levels and GBM remains unclear.

### Methods

Mendelian randomization (MR) analysis was performed using GWAS data from the UK Biobank and FinnGen databases, with fasting blood glucose, plasma glucose, cerebrospinal fluid (CSF) glucose, and diabetes as exposures. Single-cell RNA sequencing of GBM mouse models on high-glucose and control diets was conducted to explore the cellular landscape of the tumor microenvironment under hyperglycemic conditions. Additionally, gene set enrichment analysis (GSEA) was performed on transcriptomic data from brain tissues of diabetic patients to assess the activity of GBM-related pathways.

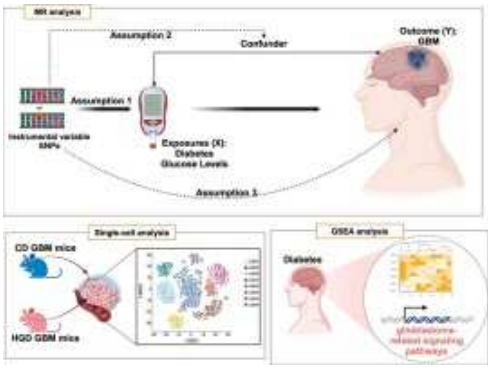
### Results

MR analysis demonstrated a significant genetic relationship between elevated fasting blood glucose and GBM risk, with an odds ratio (OR) of 40.991 (95% CI: 2.066–813.447, p=0.015). Type 2 diabetes (T2D) also showed a potential causal link with GBM, with the Weighted Median and Inverse Variance Weighted methods yielding ORs of 2.740 (95% CI: 1.033–7.273, p=0.043) and 2.100 (95% CI: 1.029–4.287, p=0.042), respectively. Single-cell transcriptomic analysis of GBM mouse models revealed an increased proportion of GBM tumor stem cells and pro-tumorigenic M2 macrophages in the high-glucose diet (HGD) group. GSEA of diabetic patient brain tissue revealed heightened activity of GBM-related pathways, particularly in astrocytes, endothelial cells, and neurons.

### Conclusion

These findings suggest that hyperglycemia may actively contribute to GBM progression by promoting cellular changes within the tumor microenvironment and activating GBM-related pathways in brain tissues.


## Graphical abstract

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## Introduction

Glioblastoma Multiforme (GBM) represents the most aggressive and common form of primary brain tumor in adults (Louis et al., 2021). Characterized by rapid growth and a high degree of malignancy, GBM tumors exhibit remarkable genetic and phenotypic heterogeneity, which complicates treatment strategies (Aldoghachi et al., 2022, Bagley et al., 2021). The metabolic microenvironment of GBM is a unique landscape shaped by the interplay between rapidly proliferating tumor cells, the brain's high demand for glucose, and the local and systemic alterations in metabolism (Elia and Haigis, 2021, Randall et al., 2020). GBM cells undergo metabolic reprogramming to support their energetic and biosynthetic needs, a phenomenon commonly referred to as the Warburg effect (Nguyen et al., 2021), wherein cancer cells favor glycolysis even in the presence of oxygen (Du et al., 2020). This metabolic shift is thought to be advantageous for the tumor cells, aiding in the evasion of apoptosis, promoting angiogenesis (Hosios and Manning, 2021), and facilitating invasion into the surrounding brain tissue (Chen et al., 2020).

The relationship between blood glucose levels and the pathogenesis of GBM has become an area of growing interest. Elevated blood glucose, commonly seen in conditions like diabetes, may exacerbate GBM's metabolic reprogramming, enhancing tumor growth, invasiveness, and resistance to therapy (Seyfried et al., 2015). Hyperglycemia has been shown to fuel glycolysis, promoting anaerobic metabolism typical of GBM, and potentially contributing to poor prognosis (Zhao et al., 2024). However, the exact role of glucose in GBM initiation, progression, and therapy response remains unclear, with conflicting evidence suggesting that factors like insulin resistance and the tumor's metabolic adaptability may mediate this relationship (Smith et al., 2018, Grasmann et al., 2021). Additionally, the influence of the blood–brain barrier on glucose transport and its impact on GBM metabolism (Mathew-Schmitt et al., 2024) is not well understood. There is a notable gap in longitudinal studies examining how fluctuations in blood glucose influence GBM progression and therapeutic outcomes, and in research exploring the molecular mechanisms by which glucose affects oncogenic pathways. Addressing these gaps could lead to novel therapeutic strategies targeting glucose metabolism, improving GBM

prognosis and treatment.

Mendelian randomization (MR) analysis (Sanderson et al., 2022, Burgess and Thompson, 2015) and single-cell transcriptomics (Butler et al., 2018) provide complementary approaches to addressing critical gaps in understanding the role of blood glucose levels in GBM progression and therapeutic response. MR analysis can establish causal relationships between hyperglycemia and GBM development by using genetic variants as instrumental variables, thus overcoming confounding factors in observational studies (Dobrijevic et al., 2023). This approach helps identify whether genetically predisposed hyperglycemia contributes directly to GBM pathogenesis and offers potential metabolic targets for intervention. On the other hand, single-cell transcriptomics enables the examination of metabolic heterogeneity within GBM tumors, identifying subpopulations with distinct glucose metabolism profiles linked to glycolytic dependence, invasiveness, and therapy resistance (Gonzalez Castro et al., 2023). By mapping gene expression patterns, this technique can reveal how hyperglycemia activates specific molecular pathways in tumor cells, shedding light on intratumoral heterogeneity (Neftel et al., 2019). Together, these methodologies can provide insights into systemic and cellular mechanisms, leading to novel biomarkers and therapeutic strategies targeting metabolic vulnerabilities in GBM.

Therefore, the aim of our study is to elucidate the genetic relationship between glucose levels and GBM progression, using Mendelian randomization to assess the systemic effects of hyperglycemia, and single-cell transcriptomics to explore the cellular and molecular mechanisms underlying glucose metabolism in GBM.

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## Section snippets

### GWAS data collections

We utilized data pertaining to “Fasting blood glucose adjusted for BMI,” “Plasma glucose levels,” “CSF glucose levels,” “Type 2 diabetes (adjusted for BMI),” and “Type 1 diabetes” sourced from the IEU Open GWAS database. The specific datasets employed were ebi-a-GCST007858, ebi-a-GCST90092819, ebi-a-GCST90025999, ebi-a-GCST007516, and ebi-a-GCST90014023, respectively, which are publicly accessible via the GWAS portal at https://gwas.mrcieu.ac.uk ↗. The datasets comprised individuals of European …

### Diabetes patient brain tissue Transcriptome data Collection

For the dataset GSE161355 (Bury et al., 2021), transcriptomic data was collected from the brain tissues of patients with diabetes as well as age and sex-matched controls. The samples were derived from six cases with self-reported diabetes within the Cognitive Function and Ageing Study neuropathology cohort, in addition to five age and sex-matched controls. This data provides transcriptomic alterations in cortical neurons, and the associated astrocytes and

endothelial cells of the neurovascular …

## Study design

MR analysis rests upon three foundational assumptions (Sanderson et al., 2022). Initially, it necessitates a robust association between the genetic variants and the exposure of interest. Subsequently, it is imperative to ascertain that these genetic variants are not confounded by any latent variables. Lastly, it is essential to validate that the influence of genetic variants on the outcome is exclusively mediated through the exposure, and not by alternative biological pathways.

As Fig. 1 shown, …

## Discussion

This study employed MR to interrogate the genetic relationships between glucose levels, diabetes, and the incidence of GBM. Our primary analysis, revealed a striking association between fasting blood glucose levels and the risk of GBM. The magnitude of this relationship suggests a potentially substantial effect of elevated blood glucose on the pathogenesis of GBM. The striking linking elevated fasting blood glucose levels with GBM risk aligns with theories that propose a hyperglycemic …

## Consent for publication

Not applicable. …

## Author contributions

JL and WJW contributed to the conception and design of this study, analysis and interpretation of data, LGY collaborated closely with BZ in project oversight. All authors read and approved the final manuscript. …

## CRediT authorship contribution statement

**Jin Li:** Writing – original draft, Visualization, Investigation, Conceptualization. **Wenjing Wu:** Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Liguo Ye:** Writing – review & editing, Validation, Supervision, Software, Project administration, Funding acquisition. **Bo Zheng:** Writing – review & editing, Validation, Investigation, Funding acquisition. …

## Ethics approval and consent to participate

Ethical review and approval can be accessed in the original studies. Informed consent was obtained from all subjects in the original genome-wide association studies. In this MR study,

only summary-level statistics were used. No identifiable private information was contained in the GWAS datasets. …

## Funding

Not applicable. …

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

Recommended articles

## References (34)

A.F. Aldoghachi *et al.*
Recent Advances in the Therapeutic Strategies of Glioblastoma Multiforme
Neuroscience (2022)

Z. Chen *et al.*
NF-kappa B interacting long noncoding RNA enhances the Warburg effect and angiogenesis and is associated with decreased survival of patients with gliomas
Cell Death Dis. (2020)

H.-C. Cheng *et al.*
Narrative review of the influence of diabetes mellitus and hyperglycemia on colorectal cancer risk and oncological outcomes
Transl. Oncol. (2021)

E. Dobrijevic *et al.*
Mendelian randomization for nephrologists
Kidney Int. (2023)

P. Du *et al.*
ANXA2P2/miR-9/LDHA axis regulates Warburg effect and affects glioblastoma proliferation and apoptosis
Cell. Signal. (2020)

T.I. Janjua *et al.*
Frontiers in the treatment of glioblastoma: past, present and emerging
Adv. Drug Deliv. Rev. (2021)

J. Liu *et al.*

Glucose metabolism of TAMs in tumor chemoresistance and metastasis
Trends Cell Biol. (2023)

C. Neftel *et al.*
An integrative model of cellular states, plasticity, and genetics for glioblastoma
Cell (2019)

S. Purcell *et al.*
PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses
Am. J. Hum. Genet. (2007)

T.N. Seyfried *et al.*
Metabolic management of brain cancer
Biochimica et Biophysica Acta (BBA) – Bioenergetics (2011)

View more references

## Cited by (0)

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