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Metabolic cross-talk between glioblastoma and glioblastoma-associated microglia/macrophages: From basic insights to therapeutic strategies

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Highlights

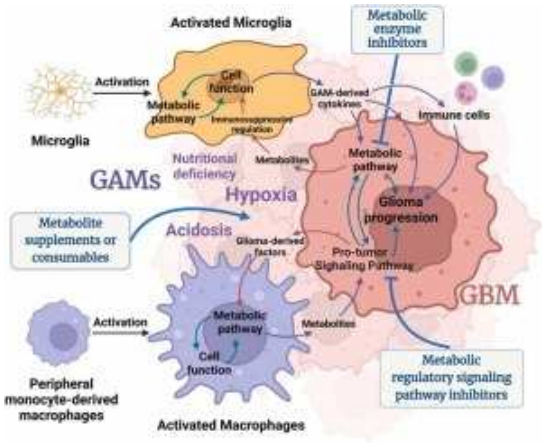
- Metabolic alterations ofglioblastoma (GBM)boosttheimmunosuppressionof GBM-associated microglia/macrophages (GAMs).

- The cytokines secreted by GBM are capable of modulating the metabolic processes of GAMs.
- GBM and GAMs form a complex network of metabolic crosstalk.
- Targeting the metabolic crosstalk between GBM and GAMs exerts anti-tumor effects.

Abstract

Glioblastoma (GBM), a highly malignant “cold” tumor of the central nervous system, is characterized by its ability to remodel the GBM immune microenvironment (GME), leading to significant resistance to immunotherapy. GBM-associated microglia/macrophages (GAMs) are essential components of the GME. Targeting GAMs has emerged as a promising strategy against GBM. However, their highly immunosuppressive nature contributes to GBM progression and drug resistance, significantly impeding anti-GBM immunotherapy. Accumulating evidence suggests that metabolic reprogramming accompanies GBM progression and GAM polarization, which are in turn driven by specific metabolic abnormalities and altered cellular signaling pathways. Importantly, metabolic crosstalk between GBM and GAMs further promotes tumor progression. Clarifying and disrupting this metabolic crosstalk is expected to enhance the antitumor phenotype of GAMs and inhibit GBM malignant progression. This review explores metabolism-based interregulation between GBM and GAMs and summarizes recent therapeutic strategies targeting this crosstalk, offering new insights into GBM immunotherapy.

Graphical Abstract



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Introduction

Glioblastoma (GBM) is a primary malignant brain tumor with a five-year survival rate lower than 10 % (Schaff and Mellinghoff, 2023). The current standard of care (SOC), including maximum safe resection combined with adjuvant temozolomide (TMZ) chemotherapy and radiotherapy, has shown no additional survival benefit for GBM patients (Jiang et al., 2021). The high heterogeneity and diffusivity make novel strategies for GBM treatment an urgent necessity. Hopefully, immunotherapy aiming to enhance the body's immune response against tumors presents a promising alternative for GBM. Common immunotherapies, including immune checkpoint inhibitors, chimeric antigen receptor (CAR)-T-cell therapy and tumor vaccines, have shown unique advantages in clinical practice for specific tumors and have demonstrated certain limitations. As the crucial immune cells within the tumor immune microenvironment, macrophages are increasingly considered promising targets in immunotherapy.

Microglia are resident macrophages and critical immune effectors in the central nervous system (CNS). After the CNS damage, peripheral monocytes also infiltrate into the brain tissue and then differentiate into macrophages (Ochocka et al., 2021). Both microglia and infiltrating macrophages, collectively known as GBM-associated microglia/macrophages (GAMs), exhibit significant plasticity upon stimulation and accumulate around the GBM (Fermi et al., 2023). In the early stage of tumorigenesis, microglia/macrophages play a positive role in immune surveillance and phagocytosis of GBM cells. With the GBM progression, recruited GAMs display a series of immunosuppressive and protumoral behaviors, including impaired antigen presentation, abnormal phagocytosis and tumor angiogenesis-promoting effects, which further promote GBM growth and invasion (Huang et al., 2022, Lepore et al., 2018). Elucidating the mechanism underlying the protumoral alteration of GAMs holds great positive significance for immunotherapies targeting GAMs.

Metabolic reprogramming allows cells to adapt to environmental stress by reshaping metabolic pathways and is crucial for tumor progression and GAM functional changes. Abnormal gene expression and altered enzyme activity lead to unique metabolic patterns in GBM (Cui et al., 2023, Larrieu et al., 2022). Hypoxia, acidosis, and accumulated metabolites caused by GBM affect the phenotype and function of cellular components within the GBM immune microenvironment (GME), including GAMs (Kloosterman et al., 2024, Wang et al., 2024). In turn, GAM metabolism influences GBM progression and is regulated by GBM. This metabolic crosstalk between GBM and GAMs ultimately induces a protumor phenotype of GAMs and accelerates GBM progression. Targeting the crucial nodes of this metabolic regulatory network represents a meaningful antitumor strategy. This review focuses on the metabolic interactions between GBM and GAMs and summarizes recent research on targeting GBM-GAM metabolic crosstalk, with the aim of providing insights for anti-GBM immunotherapy from a metabolic perspective.

Section snippets

Metabolic regulation in GBM and GAMs

Metabolic reprogramming is not only a significant hallmark of tumor progression but also a crucial process accompanying TAM phenotypic alterations. Understanding the role of metabolic reprogramming in GBM progression and GAM activation is key to developing metabolism-targeted anti-GBM immunotherapies (Fig. 1). …

Metabolic crosstalk between GBM and GAMs

The cellular components in the GME have an intricate interplay. GBM and GAMs can impact each other's proliferation or immune functions through metabolic processes (Fig. 2). In turn, their metabolic processes are also regulated by each other's signaling molecules (Fig. 3). Clarifying the metabolic crosstalk between GBM and GAMs provides valuable research directions. …

Targeting GBM and GAMs metabolic crosstalk as antitumor strategies

As mentioned, there are multiple immunometabolic regulatory targets between GBM and GAMs. Current strategies mainly focus on the metabolism-related targets, including key enzymes, metabolites, and signaling pathways. Small molecule inhibitors, RNA interference, and drug delivery systems are used to modulate these targets to combat GBM (Table 1). …

Conclusion and prospects

The metabolic crosstalk between GBM and GAMs leads to an immune-suppressive microenvironment, further promoting GBM progression. As a widely existing regulatory process in GBM and immune cells, metabolic reprogramming provides a new intervention avenue for GBM treatment.

The anti-GBM treatment targeting the metabolic crosstalk between GBM and GAMs can be summarized into three strategies: metabolic enzymes modulation, metabolites regulation and metabolism-related signaling pathway regulation. …

Ethics approval

Not applicable …

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CRediT authorship contribution statement

Yuan Gao: Conceptualization, Writing-original draft, Writing-review and editing. **Mengxia Zhang:** Conceptualization, Writing-original draft, Writing-review and editing. **Guihua Wang:** Visualization, Writing-review and editing. **Weiwei Lai:** Visualization, Writing-review and editing. **Shuxian Liao:** Investigation, Methodology, Writing-review and editing. **Yao Chen:** Investigation, Methodology, Writing-review and editing. **Qian Ning:** Conceptualization, Funding acquisition, Supervision, Writing-review and …

Declaration of Competing Interest

The authors declare that they have no competing interests. …

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Some of the figures in this article were created with BioRender.com. …

Consent to participate

Not applicable …

Consent to publish

Not applicable …

Yuan Gao, Ph.D. candidate in tumor pharmacology with experience in laboratory projects. The main research projects involve the pharmacological experimental studies on oncology and neuroscience. …

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