Advances in Treatment Approaches for IDH Wild-Type Glioblastoma

Yunxi Yao

Fujian Medical University, Fuzhou, China

Abstract. IDH-wild-type glioblastoma (WHO CNS Grade IV; known as glioblastoma multiforme, GBM) is the most malignant and recurrent brain tumor in the central nervous system. Research on GBM primarily focuses on its mechanisms and immunotherapy. However, due to cold tumor characteristics such as the immunosuppressive tumor microenvironment (TME), blood-brain barrier (BBB) obstruction, and tumor heterogeneity, immunotherapy regimens remain in the clinical trial phase. Overcoming core challenges including BBB barrier, TME, and tumor proliferation, invasion, and migration is urgently needed. The review focuses on the molecular mechanism and comes up with target strategy. The core components in these JAK/STAT, RAGE pathway are one of most important and efficient sites which has a potential inhibiting GBM. In terms of strategy of sorting out BBB, CL5B targets claudin-5 to reversibly open BBB. Together with approaches such as the FG-PIC system, this strategy has demonstrated encouraging efficacy and provides a potential route to overcome BBB-associated drug resistance. Moreover, the combination of acriflavine and photodynamic therapy (PDT) increases $CD8^+$T-cell infiltration by approximately 1.3-fold and markedly alleviates the immunosuppressive TME. These effects suggest a feasible strategy to address therapeutic resistance caused by both BBB limitation and TME-driven immune suppression. Overall, treatment strategies aimed at the “cold tumor” features of glioblastoma (GBM) offer new perspectives for GBM therapy.

Keywords: Glioblastoma Multiforme, Blood-Brain Barrier, Tumor Microenvironment.

1. Introduction

IDH wild-type glioblastoma (WHO CNS Grade IV; formerly known as glioblastoma multiforme, GBM) originates from astrocytes. It is the most aggressive, hardest to eradicate, and has the poorest prognosis among primary brain tumors. The annual incidence of glioblastoma multiforme (GBM) is 3–4 per 100,000, accounting for 48% of all primary central nervous system (CNS) malignancies [1]. The fifth edition (2021) of the World Health Organization (WHO) classification of central nervous system (CNS) tumors redefines diagnostic criteria (prioritizing molecular features over morphological characteristics) and classifies GBM as IDH wild-type glioblastoma (WHO CNS Grade IV) which corresponds tothe highest grade among malignant CNS tumor [2]. GBM is highly invasive and has a naturally immunosuppressive microenvironment, which limits surgical resection and makes curative surgery impossible. Its characteristics are a high recurrence rate, high drug resistance, and short survival after surgery. The median age at diagnosis is 65 years, and the median survival period is 15 months. The 2-year overall survival (OS) rate after combination therapy with radiotherapy (RT) and temozolomide (TMZ) is 26.5% [1].Among the main current treatment approaches, there are three primary methods: the standard Stupp regimen, form-based electric field therapy, and immunotherapy. Stupp used pathological diagnosis and combined radiotherapy, chemotherapy, and TMZ therapy to assess the methylation level of MGMT (O6-methylguanine-DNA methyltransferase, which promotes tumor cell survival and drug resistance). Based on this assessment, the feasibility of reintroducing a treatment regimen for recurrence was determined. This approach is consistent with standard tumor treatment, but high drug resistance and low chemotherapy efficacy remain serious problems. In the treatment of glioblastoma with electrotherapy, electrode arrays are used to create an alternating electric field that causes cell death by interrupting the mitosis process in tumor cells. For example, it inhibits the assembly of mitotic microtubules. In a Phase III clinical trial combining electrotherapy with TMZ, the median progression-free survival (PFS) increased by 3.1 months (from 4.0 to 7.1 months), and the five-year survival rate increased by 8% (from 5% to 13%) [3]. However, this

approach presents several problems, including limited potential for long-term healing, the need for patients to adhere strictly to treatment, and significant variability in therapeutic outcomes due to individual differences. Immunotherapy for GBM encompasses various therapeutic targets and approaches, with the potential to achieve favorable clinical outcomes when combined with other therapies recognized in clinical practice. However, despite this potential for development, the paralysis of the immune system resulting from the characteristics of "cold tumors" hinders the optimization of therapeutic efficacy and prevents further successes and the overcoming of barriers encountered in clinical trials. Therefore, this highly invasive, drug-resistant, and immunosuppressive microenvironment remains a significant challenge in the treatment of GBM, requiring urgent solutions. This scientific paper focuses primarily on the latest advances and discoveries in the treatment of GBM through three therapeutic approaches: anti-invasive metastasis (molecular technologies), drug resistance (Blood-Brain Barrier, BBB), and transformation of the immunosuppressive tumor microenvironment (TME). Finally, we briefly summarize potential directions for future research in the development of treatments for GBM.

2. Molecular Mechanisms and Targeted Therapies

GBM is not the result of a single pathway or signaling influence, but rather the outcome of multiple factors interacting with one another. For example: JAK/STAT, RAGE (Janus kinase receptor and transcription activator), EGFR (epidermal growth factor receptor), PI3K/AKT, NF-κB (nuclear factor-κB signaling pathway), VEGF (vascular endothelial growth factor), TGF-β (transforming growth factor-β). In recent years, the discovery of targets and novel therapies has provided new approaches and treatment strategies for GBM.

2.1. JAK/STAT Signalling Pathway

The JAK/STAT signalling pathway comprises the tyrosine kinase receptor, the tyrosine kinase JAK (Janus kinase), and the transcription activator STAT (Signal Transducer and Activator of Transcription) as its principal components. In the tumor microenvironment, abnormal and excessive activation of receptor tyrosine kinases (RTKs) stimulates JAK kinase activation. Activated JAK kinases become phosphorylated and bind to STAT proteins, thereby increasing the expression of anti-apoptotic proteins such as Bcl-2 and promoting the expression of genes such as cyclin D1. This process enhances cell proliferation and resistance to apoptosis. Furthermore, it increases the expression of MMP-2 and MMP-9 metalloproteinases, promoting tumor invasion and metastasis.

In the hypoxic microenvironment of the tumor, the increased expression of the hypoxia-induced transcription factor HIF-1αamplifies the JAK/STAT3 signaling pathway, which increases the self-renewal capacity of glioblastoma stem cells (GSCs). This promotes the secretion of immunosuppressive factors, such as IL-10 and TGF-β. It inhibits the maturation of dendritic cells in immune cells, prevents T cell activation, and promotes their M2 phenotype which contributes to cancer progression. This phenotype contributes overall to the creation of an immunosuppressive microenvironment. Considering the critical role that the JAK/STAT3 signaling pathway plays in the development of GBM, several studies have shown that ruxolitinib inhibits IL-6/STAT3 phosphorylation. It has also been shown that TMZ increases apoptosis and thus suppresses tumor growth. In contrast, AG490, which has a high risk of side effects, is a JAK inhibitor that suppresses the biological activity of STAT3, inhibiting GBM migration and invasion and subsequently reducing the levels of several anti-apoptotic proteins. However, it is difficult to move on to the clinical trial phase. Arunotinib is a pan-JAK inhibitor that acts on the JAK2/STAT3 signaling pathway to inhibit angiogenesis. In combination with TMZ, it improves treatment outcomes [4].

2.2. RAGE signalling pathway

RAGE (Receptor for Advanced Glycation End Products) acts as a multiligand receptor in the development and progression of GBM. It not only promotes tumor invasion and proliferation but also

creates an immunosuppressive TME. Meanwhile with its function as a multi-ligand receptor, it also stimulates angiogenesis and hypoxia adaptation, mediates resistance to therapy and exacerbates encephalitis, oxidative stress, and neurological damage. RAGE plays a central regulatory role in glioblastoma progression and cognitive decline. Its primary function involves binding to relevant ligands through adaptor proteins such as DIAPH1, TIRAP, and MyD88, activating downstream pathways including NF-κB, JAK/STAT, MAPK, and PI3/Akt. This initiates a "Ligand-RAGE-Downstream Pathway" cascade that drives glioblastoma progression and neurotoxicity (Table 1).

Table 1. Ligand-RAGE-downstream pathway-mechanism of action matrix

Activation pathway	Intervening factors and pathways	Impact
PKC (protein kinase C)	NADPH oxydase, NF-κB, etc.	Angiogenesis and Invasion
NADPH oxidase/reactive oxygen species	PTEN, MMPs, VEGF, ROS, etc.	
mTOR	S6k, 4E-BP1, IL-6, TNF-α, NADPH, etc.	The Formation and Regulation of the Immunosuppressive Microenvironment
TGF-β/Smad	p21, p27, Snail, ZEB, MMPs, α-SMA, CTGF, Bim, VEGF, etc.	
JAK/STAT	Bcl-2, Cyclin D1, IL-6, VEGF, etc.	
MAPK	TNF-α, IL-6, IL-1β,etc.	
PI3K/Akt	Akt, mTOR, FOXO, GSK-3β, Bad, p21, p27, NF-κB, ect.	Proliferation, Migration, and Invasion
NF-κB	COX-2, disruption of the blood-brain barrier, etc.	
Rho GTPase (Rac1, Cdac 42)	PAKs, MAPK, p38, NF-κB, PI3K/AktCyclin D1, IL-6, etc.	
Wnt/β-catenin	Cyclin D1, c-Myc, etc.	Drug resistance, Maintaining cellular pluripotency

Current therapies targeting RAGE generally focus on its ligands. Drugs that target RAGE compete for binding to the ligand binding sites, inhibit NF-κB, and reduce glioblastoma growth. SRAGE, a decoy receptor, could block the signaling pathway, inhibit the formation of new tumor blood vessels and alleviate neuroinflammation by competing with the ligands for binding. Phytochemical compounds hold great promises for modulating RAGE. Danthinone IIA inhibits the RAGE–NF-κB pathway, thereby suppressing glioblastoma growth and proliferation. Curcumin and berberine regulate the HMGB1–RAGE interaction and expression to improve the cognitive impairment [5].

3. Breaching the blood-brain barrier (BBB)

In the treatment of GBM, the blood-brain barrier (BBB) impedes the entry of the vast majority of drugs into the intracranial space. As a result, the beneficial concentration falls below the level necessary to ensure therapeutic efficacy, reducing the drug's effectiveness. In recent years, several effective treatments have been developed to cross the BBB, including the use of nanoparticles and biohybrids to open the BBB and improve drug delivery.

3.1. CL5B specifically targets Claudin 5 (CLDN 5)

Claudin 5 is an important protein that supports the tight connections between endothelial cells in the BBB. Studies have shown that the small molecule CL5B directly targets CLDN5 and relocates it at the junction to weaken the connection and create small gaps between cells. This temporarily opens the BBB for less than 30 minutes, which is reversible and depends on the concentration of CL5B in the blood [6].

3.2. FG (biological glue) as a PIC (photochemical internalisation) local delivery system

By enhancing drug toxicity via PCI to bypass the blood-brain barrier for GBM treatment, effective local drug delivery without degradation was achieved, demonstrating significant growth inhibition.

FG (fibrinogen mixed with thrombin at a 1:1 ratio) exhibits no additional toxicity and demonstrates strong clinical compatibility. It can simultaneously load the chemotherapeutic agent BLM (bleomycin) and the photosensitiser ALPcS2a (aluminium phthalocyanine disulfonate) to enter tumour cells via endocytosis. ALPcS2a is located on the endomembrane, whilst BLM is encapsulated within the endosomal lumen. Photostimulation at 670 nm activates ALPcS2a, disrupting the endomembrane to allow BLM to escape from the endosome into the cytoplasm. Here, BLM directly acts upon DNA, enhancing cytotoxicity whilst circumventing drug degradation by lysosomes. The comparative trial results demonstrated that ,compared with free drug, the PCI effect of drugs released via FG showed no significant difference [7].

4. Targeting the DLEU1 Functional Chain

DLEU1 (long noncoding RNA, lncRNA) activates heat shock factor 1 (HSF1), stimulating the secretion of transforming growth factor β (TGF-β) and interleukin-6 (IL-6) by cancer-associated fibroblasts (CAFs), thereby forming a positive feedback loop. Meanwhile, it alters the TME by promoting the M2 polarization of TAM and increasing the number of regulatory T cells (Treg), and reducing the infiltration of CD8+ T cells. DLEU1 is an significant factor causes GBM infiltration and drug resistance [8].

Compared to the negative control (NC) group, the DLEU1 expression in the knockdown lncRNA DLEU1 group reduced to one-sixth to one-fifth. In this model, the knockdown group cultured for 24 hours noticeably reduced the skills of invasion and migration. After 96 hours of culture, GBM cell proliferation decreased to nearly one-third. Combination treatment with siRNA-DLEU1 and 200 μM TMZ increased the sensitivity of GBM to chemotherapy by 10% to 20%. This discovery has identified DLEU1 as a potential biomarker for TMZ resistance in GBM treatment. Though clinical data are restricted, this chemotherapy approach is promising. It holds significant potential for enhancing cell sensitivity to chemotherapy and strengthening antitumor immune responses, which offers a potentially innovative and hopeful treatment option for GBM [9].

The Warburg effect, glutamine metabolism, and lipid metabolism play a role in metabolic reprogramming that strengthens immunosuppression. This leads to M2 polarization of TAM and metabolic changes in immunosuppressive cells such as myeloid-derived suppressor cells (MDSC). For this reason, targeting key factors of metabolic reprogramming may directly enable immunotherapy by preventing the immunosuppressive microenvironment from converting the “cold tumor” into a “hot tumor” [10].

A study on the glutaminase (GA) inhibitor CB-839 shows that GLS inhibitors suppress GBM cell proliferation by modulating important metabolites. Specifically, CB-839 weakens the redox reaction of α-KG (α-ketoglutarate), an important energy source in the tricarboxylic acid cycle, thereby inhibiting the cycle and slowing GBM progression. Experimental data showed that, compared to the control group, fragmentation markers decreased by one-sixth in T98G cells, one-fourth in LN229 cells, and one-third in U87MG cells. In the test based on cell lines, treatment with 1 μM CB-839 for four days resulted in a decrease in proliferation rate compared to the control group treated with DMSO. T98G and LN229 cells showed about a two-thirds reduction in proliferation compared to the DMSO group, while U87MG cells displayed only a one-quarter reduction. This inhibitor exhibits a clear antiproliferative effect against GBM cells. However, clinical evidence is limited, and its safety and efficacy have not yet been fully confirmed [11].

5. Conclusion

In summary, new inhibitors acting on the main molecular signaling pathways of GBM are appearing on the market. Nanotechnology, which effectively crosses the blood-brain barrier (BBB), is very promising as a new therapeutic strategy against GBM. Combined treatments adapted to the TME offer significant advantages.

Existing research has deepened our understanding of the molecular mechanisms involved, but the complex interactions between the different GBM signaling pathways remain poorly understood. Most of this research still suffers from a lack of data from clinical studies, and barriers such as the blood-brain barrier (BBB) and the TME remain major challenges for their clinical application, which causes problems such as poor efficacy and high recurrence rates and stuff like that. Technological advances aimed at overcoming the BBB have already yielded promising results, and excellent ability to cross the blood-brain barrier has been confirmed in vitro and in vivo experiments. The vast majority of current treatments remain in phase I/II clinical trials, and some have not yet undergone feasibility and safety assessments. Besides, existing production technologies are not suitable for the large-scale production required to meet clinical demand. Combined therapies targeting the tumor microenvironment furnish significant advantages in suppressing tumor proliferation and reshaping the tumor microenvironment. Even so, the fundamental mechanisms of the tumor microenvironment remain unclear, which is lack of clinical data. Apart from this, the efficacy and safety of these treatments have not yet been proven.

In the future, researchers will need to investigate the mechanisms inherent GBM progression and TME formation in greater detail, where they can precisely identify the most essential therapeutic targets. At the same time, the clinical feasibility and safety of most of these treatment approaches have not yet been confirmed. The large-scale production of drugs needed further technological advances, so that the drugs can cross the BBB. In the coming years, combination therapies will also become the most crucial treatment approach. The limitations of single-agent therapies can be overcome by integrating targeted molecular strategies, techniques for crossing the blood-brain barrier, and treatments targeting the tumor microenvironment. This paves the way for more effective management of GBM and offers broad clinical potential.

References

[1] Jezierzański, M., Nafalska, N., Stopyra, M., Furgoł, T., Miciak, M., Kabut, J., Gisterek-Grocholska, I. (2024). Temozolomide (TMZ) in the Treatment of Glioblastoma Multiforme—A Literature Review and Clinical Outcomes. Current Oncology, 31(7), 3994–4002.

[2] Gritsch, S., Batchelor, T. T., Gonzalez Castro, L. N. (2021). Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. Cancer, 128(1), 47–58.

[3] Ferri, A., Contadini, C., Di Girolamo, C., Cirotti, C., Fiscon, G., Paci, P., Marzullo, M., Gentileschi, M. P., Yamamoto, T., Strauss, R., Del Bufalo, D., Ciapponi, L., Barilà, D. (2026). Caspase-8 is a novel modulator of Homologous Recombination Repair in response to ionizing radiations in glioblastoma. Cancer Letters, 637, 218120.

[4] Mao, Q., & Ju, H. T.. (2025). Research progress on JAK/STAT signaling and neuroastroma. Advances in clinical medicine., 15(5), 2632-2640.

[5] Raj, J. A. T., John, G., Ghanekar, S., Thiruselvan, G. K., Shah, J., Ande, D., Chatterjee, A., Goda, J. S. (2025). RAGE signaling pathway in glioblastoma and cognitive decline: Insights into inflammatory mechanisms and therapeutic implications. Brain Research, 1869, 150026.

[6] Inoue, S., Shirakura, K., Shirono, A., Taguchi, J., Ikeda, Y., Tomita, S., Funatsu, R., Muraoka, K., Hashimoto, Y., Tachibana, K., Hino, N., Doi, T., Ikemi, Y., Nunomura, K., Lin, B., Nakagawa, S., Tsujikawa, K., Tanaka, S., Obana, M., … Okada, Y. (2025). Claudin 5-binding small molecule transiently opens the blood-brain barrier and safely enhances brain drug delivery. Journal of Controlled Release, 388, 114314.

[7] Madsen, S. J., Devarajan, A. G., Chandekar, A., Nguyen, L., Hirschberg, H. (2023). Fibrin glue as a local drug and photosensitizer delivery system for photochemical internalization: Potential for bypassing the blood-brain barrier. Photodiagnosis and Photodynamic Therapy, 41, 103206.

[8] Rajabi, A., Malek-Abbaslou, E., Alipour-Khezri, E., Safaralizadeh, R. (2025). DLEU1 as a key regulator in glioblastoma: A review of ferroptosis resistance, tumor microenvironment interactions, and emerging RNA-based therapeutic strategies. International Journal of Biological Macromolecules, 332, 148554.

[9] Lv, Q.-L., Wang, L.-C., Li, D.-C., Lin, Q.-X., Shen, X.-L., Liu, H.-Y., Li, M., Ji, Y.-L., Qin, C.-Z., Chen, S.-H. (2020). Knockdown lncRNA DLEU1 Inhibits Gliomas Progression and Promotes Temozolomide Chemosensitivity by Regulating Autophagy. Frontiers in Pharmacology, 11.

[10] Cortes Ballen, A. I., Amosu, M., Ravinder, S., Chan, J., Derin, E., Slika, H., Tyler, B. (2024). Metabolic Reprogramming in Glioblastoma Multiforme: A Review of Pathways and Therapeutic Targets. Cells, 13(18), 1574.

[11] De los Santos-Jiménez, J., Rosales, T., Ko, B., Campos-Sandoval, J. A., Alonso, F. J., Márquez, J., DeBerardinis, R. J., Matés, J. M. (2023). Metabolic Adjustments following Glutaminase Inhibition by CB-839 in Glioblastoma Cell Lines. Cancers, 15(2), 531.