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Glioblastoma: Molecular features, emerging molecular targets and novel therapeutic strategies

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Highlights

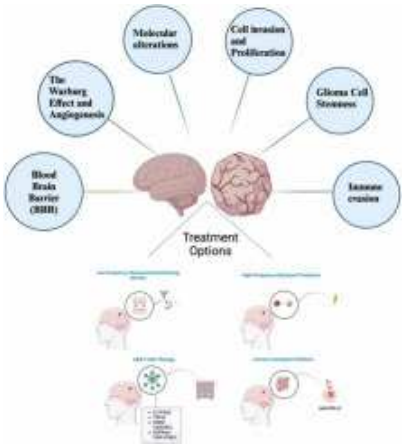
- Characteristic molecular features contribute to GBM pathophysiological mechanisms
- Specialized ultrasound-assisted drug delivery overcomes GBM drug resistance
- CAR T-cell administration and adaptive immune modulation exert GBM immunotherapeutic effects
- Emerging molecular targeted schemes involve altered RTK pathways and epigenetic mechanisms

Abstract

Glioblastomas (GBMs) constitute the most common malignant tumors of the Central Nervous System (CNS) with a complex molecular, genetic and histological profile and extensive heterogenicity. GBMs are notoriously difficult to treat, with morbidity and mortality rate that remain high and practically unchanged, despite the aggressive and multimodal treatment

strategies. Keeping up with current research and emerging scientific data is of primary importance for the detection of new molecular targets, enabling the design of novel therapeutic strategies. Herein, we discuss current data on the cellular and molecular features that contribute to GBM pathophysiological mechanisms in an effort to reveal emerging molecular targets with therapeutic potential as well as effective immunotherapeutic approaches, including chimeric antigen receptor (CAR) T-cell therapy and adaptive immune modulation with immune checkpoint inhibitors. Enhanced drug delivery strategies such as ultrasound-assisted technologies to overcome drug resistance are also discussed, aiming to provide an overall translational perspective that bridges molecular insights with practical therapeutic implications.

Graphical abstract



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Introduction

Glioblastomas (GBMs) are highly malignant and invasive neoplasms, accounting for approximately 60–70 % of gliomas. Epidemiologically, GBMs are more frequent in men with a median age of diagnosis at 65 years (Davis, 2018, Wang et al., 2023). According to the Central Brain Tumor Registry of the United States (CBTRUS) statistical report of 2016–2020, gliomas represented the 26.3 % of all CNS tumors, whilst GBMs account for the 50.9 % of all malignant CNS tumors and 14.2 % of all CNS tumor types. The incidence and prevalence of gliomas and glioblastomas in particular, remains stable compared to the CBTRUS report of 2015–1019 with malignant gliomas accounting for 5 cases per 100.00 people and 14.000 new GBM patients yearly (Ostrom et al., 2022, Ostrom et al., 2023, Wang et al., 2023).

Based on the latest 2021 WHO CNS5 classification of gliomas, IDH-wildtype glioblastoma accounts for the 95 % of grade 4 astrocytomas, being more frequent in patients older than 55 years. The IDH-mutant grade 4 astrocytoma (about 5 % of cases) predominates in younger patients or those with prior lower-grade diffuse glioma. Histologically, GBMs are characterized by marked hypercellularity, nuclear atypia, microvascular proliferation and necrosis. From a

molecular standpoint, they are characterized by significant heterogenicity, with various genetic and epigenetic alterations driving tumor progression: Telomerase Reverse Transcriptase (*TERT)* promoter mutations (~80 %), Epidermal Growth Factor Receptor (*EGFR)* amplification (~50 %), *PTEN* loss (~40–50 %), *CDKN2A/B* deletion, ATRX and H3K27 mutations and chromosome + 7/-10 mutations are typical. The presence of molecular mutations of *TERT* promoter, *EGFR* and chromosome + 7/-10 set the diagnosis of glioblastoma, even in the absence of typical histological features such as microvascular proliferation and mitosis. Microscopically, there are five different types of GBMs that have been recognized, namely, the small cell type, granular cell type, epithelioid cell type, giant cell type and sarcomatous type. Each of these types is distinguished by various histological and molecular properties (Smith et al., 2022).

Interestingly, the molecular background of gliomas has been correlated with their imaging features, aiding immensely to GBM diagnosis. Increased cellularity and relative Cerebral Blood Volume (rCBV) upon Apparent Diffusion Coefficient (ADC) and CBV map is observed respectively, while upon T2 and FLAIR-weighted images, GBMs are highly characterized by heterogenous enhancement with areas of necrosis and peripheral ring enhancement (Park et al., 2023).

The median survival of GBM patients is less than a year, whilst standard treatment with surgery followed by radiotherapy has a mean benefit of 24 months in overall patients' survival. The updated treatment protocol of maximal safe resection followed by radiotherapy and chemotherapy with concomitant and adjuvant temozolomide (TMZ) has offered a 14.6-month median survival and 37 % in morbidity rate (Stupp et al., 2005, Fig. 1).

In this review, we provide an update on the main areas of research in glioblastomas, highlighting the key molecular vulnerabilities and emerging targets. We further progress to novel therapeutic strategies including immunotherapy and enhance drug delivery technologies that offer potential for improving patient management and survival outcomes. This is an essential review given the rapidly evolving landscape of glioblastoma research, where new molecular insights and therapeutic approaches are continuously emerging. Unlike other articles, this work uniquely integrates recent findings from both preclinical and clinical studies, offering a translational perspective that bridges molecular insights with practical therapeutic implications, further serving as a valuable resource for clinicians, researchers and students. The comprehensive and up-to-date overview will benefit the readers by enhancing their understanding of glioblastoma pathogenesis and also provide valuable information on the development and application of more effective, personalized treatment modalities.

Section snippets

Cellular and molecular insights of glioblastomas pathology

The complexity of GBM lies in its genetic heterogeneity and the tumor microenvironment (TME), which supports immune evasion and resistance to treatment. Advances in multi-omic approaches have further clarified the interaction between tumor cells and the immune system, including tumor-associated macrophages (TAMs) and immune-suppressive pathways, such as those involved in T-cell exhaustion (Strepkos et al., 2020).

The brain TME consists of various cell types including myeloid cells, TAMS, …

Emerging molecular targets for glioblastomas

Taking into account the molecular alterations characterizing cancer cells, several molecular vulnerabilities have been determined, including altered receptor tyrosine kinase (RTK) pathways and epigenetic mechanisms, providing opportunities for targeted therapies. RTKs promote oncogenesis through amplification, ligand-domain mutations, and chromosomal translocations, primarily activating the Ras/MAPK, PI3K/AKT/mTOR, and FAK/Src pathways. RTK overexpression in gliomas has been previously …

Innovative immunotherapeutic approaches in glioblastomas

In addition to molecular targeting, adaptive immunotherapy approaches that can combine checkpoint inhibitors with tumor microenvironment modifiers, are currently exploited to overcome GBM's resistance to immune attacks. In this section, we provide evidence of the adaptive immune modulation efficacy and the CAR T-cell therapy application in glioblastomas. …

Enhanced drug delivery approaches in glioblastomas

Latest developments in ultrasound technology have advanced chemotherapy and immunotherapy delivery across the BBB, enhancing immune recognition and tumor microenvironment modulation. Focused ultrasound (FUS), widely used for essential tremor and Parkinson's disease, is now being applied to CNS tumors (Elias et al., 2016, Moosa et al., 2019).

Bunevicius et al. (2020) demonstrated that FUS efficacy in brain tumors depends on its interaction with BBB permeability via high- and low-intensity …

Conclusion and future perspectives

Glioblastoma remains a formidable therapeutic challenge due to its genetic heterogeneity, treatment resistance, and immunosuppressive TME. Advances in signaling pathways and molecular mechanisms have led to the identification of biomarkers with potential therapeutic significance. Despite progress in immunotherapy, monotherapy with a single immune checkpoint inhibitor (ICI) has demonstrated limited efficacy. Combination strategies integrating multiple ICIs with chemotherapy and radiotherapy …

CRediT authorship contribution statement

Christina Piperi: Conceptualization, Writing – original draft, Writing – review & editing. **Anastasios Politis**: Writing – original draft, Writing – review & editing. **Lampis Stavrinou**: Writing – review & editing. **Aristotelis Kalyvas**: Writing – review & editing. **Efstathios Boviatsis**: Writing – review & editing. …

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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. …

Anastasios Politis, M.D., MSc., Neurosurgery Resident at the 2nd Department of Neurosurgery in NKUA, with a special focus on neuro-oncology and functional neurosurgery. His current research is focused on studying novel signaling pathways involved in the pathogenesis of gliomas as well as identification of new biomarkers for their diagnosis and treatment. …

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References (143)

P. Andre *et al.*
Anti-NKG2A mAb Is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK Cells
Cell (2018)

B. Badie *et al.*
Expression of Fas ligand by microglia: Possible role in glioma immune evasion
J. Neuroimmunol. (2001)

A.C. Carvalho da Fonseca *et al.*
Increased expression of stress inducible protein 1 in glioma-associated microglia/macrophages
J. Neuroimmunol. (2014)

C.-S. Chiang *et al.*
Tumor cell-targeting radiotherapy in the treatment of glioblastoma multiforme using linear accelerators
Acta Biomater. (2021)

M.E. Davis
Epidemiology and Overview of Gliomas
Semin Oncol. Nurs. (2018)

M.-D. Filippi
Mechanism of diapedesis
Import. Transcell. Route Adv. Immunol. (2016)

X. Gu *et al.*
PRMT1 is an important factor for medulloblastoma cell proliferation and survival
Biochem Biophys. Rep. (2022)

V. Kumar *et al.*
The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment
Trends Immunol. (2016)

E. Kunadis *et al.*
Targeting post-translational histone modifying enzymes in glioblastoma
Pharm. Ther. (2021)

J.H. Park *et al.*
CD19-targeted CAR T-cell therapeutics for hematologic malignancies: interpreting clinical outcomes to date
Blood (2016)

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Cited by (0)

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Aristotelis Kalyvas, MD, MSc, PhD, Assistant Professor of Neurosurgery and a surgical neuro-oncologist at NKUA. He specializes in glioma and intra-axial tumor surgery, brain mapping, and both open and endoscopic skull base surgery. He completed a two-year clinical fellowship at the University Health Network and the University of Toronto. He holds a MSc from the University of Edinburgh and a PhD in structural brain connectivity and white matter anatomy. He has authored over 90 publications, with a focus on connectivity-informed approaches to tumor surgery. His current research includes multiparametric brain mapping, TMS, HIFU, and liquid biopsies in glioma care.

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