ScienceDirect

Cancer Letters

Volume 617, 1 May 2025, 217601

Advancing glioblastoma therapy: Learning from the past and innovations for the future

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Received 14 November 2024, Revised 25 February 2025, Accepted 1 March 2025, Available online 2 March 2025, Version of Record 11 March 2025.

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Highlights

- GBM is driven by genetic mutations, dysregulated signaling pathways, and a hostile tumor microenvironment.
- Cancer neurosciences provide insights into cancer-nerve interplay which shapes GBM progression.
- Immunotherapy, oncolytic viral therapies, and cancer vaccines are undergoing clinical-stage explorations.
- Emerging signaling pathways involved in GBM initiation and progression need to be targeted to design GBM therapeutics.

- Multi-omics profiling, biomarker-driven therapy, and combination therapies are expected to improve GBM prognosis.

Abstract

Marred by a median survival of only around 12–15 months coupled with poor prognosis and effective therapeutic deprived drug armory, treatment/management of glioblastoma has proved to be a daunting task. Surgical resection, flanked by radiotherapy and chemotherapy with temozolomide, stands as the standard of care; however, this trimodal therapy often manifests limited efficacy due to the heterogeneous and highly infiltrative nature of GBM cells. In addition, the existence of the blood-brain barrier, tumor microenvironment, and the immunosuppressive nature of GBM, along with the encountered resistance of GBM cells towards conventional therapy, also hinders the therapeutic applications of chemotherapeutics in GBM. This review presents key insights into the molecular pathology of GBM, including genetic mutations, signaling pathways, and tumor microenvironment characteristics. Recent innovations such as immunotherapy, oncolytic viral therapies, vaccines, nanotechnology, electric field, and cancer neuroscience, as well as their clinical progress, have been covered. In addition, this compilation also encompasses a discussion on the role of personalized medicine in tailoring treatments based on individual tumor profiles, an approach that is gradually shifting the paradigm in GBM management. Endowed with the learnings imbibed from past failures coupled with the zeal to embrace novel/multidisciplinary approaches, researchers appear to be on the right track to pinpoint more effective and durable solutions in the context of GBM treatment.

Introduction

Glioblastoma, also known as malignant glioma, is a highly aggressive, recurrent, and common primary brain tumor in adults [1]. The World Health Organization 2021 guidelines classified Glioblastomas as grade IV astrocytoma, with major histopathology features being necrosis and endothelial proliferation, wildtype isocitrate dehydrogenase (IDH)- tumors that are devoid of IDH mutations, and histone H3-3A mutations [2]. GBM pertains to the frontal or temporal lobes of the brain with scarce chances of occurrence in the brainstem, cerebellum, or spinal cord [3]. The causative parameter of GBM is unknown; however, exposure to ionizing radiation is considered the most prominent causative agent for GBM [4]. Also, specific genetic syndromes like neurofibromatosis, tuberous sclerosis, lynch syndrome, Li-Fraumeni, susceptibility to allergy, and impaired immune response are associated with an increased risk of GBM [5,6]. Unfortunately, these tumors are highly devastating, representing 45% of all gliomas, with a 5-year relative survival rate of only 5%. The median age of diagnosis is 64 years, and males are more commonly affected than females (1.7:1 ratio) [7,8]. Patients diagnosed with malignant gliomas face a grim prognosis, often succumbing to the disease within a year [9,10]. Glioblastoma exhibits cellular and morphological diversity, originating from neuroglial stem cells or progenitor cells with some somatic molecular defects [11]. The tumor has three main regions: a necrotic

central area, a proliferative and angiogenic region, and the surrounding brain where invasive tumor cells escape [12]. Unfortunately, one-third of patients may have multiple foci lesions, making the prognosis worse due to challenges in surgical removal [13].

Generally, there are two types of glioblastomas, i.e., primary (*de novo*) and secondary. Primary glioblastoma is more common in elderly patients and develops without prior signs of a precursor malignant lesion. Secondary glioblastoma originates from lower-grade gliomas and progresses to Grade IV, occurs in younger patients generally with IDH mutations, has less necrosis, and has a better prognosis when compared to primary GBM [14,15]. Additionally, IDH-wild-type glioblastomas are classified into three molecular subtypes based on their DNA methylation profiles and mutations: Receptor tyrosine kinase (RTK1), RTK2, and mesenchymal [16] -with RTK1 linked to Platelet-derived growth factor receptor alpha (PDGFRA) amplification, RTK2 to Epidermal growth factor receptor (EGFR) amplification, and mesenchymal to Neurofibromatosis type 1 (NF1) mutations [17,18]. Transcriptomic analyses further align these methylation-based subtypes with gene expression profiles, categorizing GBM into proneural (RTK1), classic (RTK2), and mesenchymal groups [19,20] and this integrated classification highlights the convergence of genetic, epigenetic, and transcriptional alterations in GBM subtyping.

This review discusses the complexity of GBM pathology and the influence of the tumor microenvironment (TME) on GBM progression, which impedes the development of effective treatments. It highlights how GBM cells exploit the nervous system for invasion, contributing to its plasticity. Furthermore, a discussion on limited treatment modalities for GBM, resistance to the present therapeutics, other challenges encountered in treatment, and future therapeutic aspects have been incorporated. Also, potential strategies to overcome the hurdles in GBM treatment and improve treatment outcomes have been discussed briefly. Notably, the novel therapeutic approaches covered in this review have been categorized based on signaling pathways to facilitate the development of more personalized treatment strategies.

Section snippets

Genetic alterations

Glioblastomas are generally characterized by the absence of mutations in H3-3A and the presence of wild-type IDH [2]. Common genetic/molecular alterations include gains in chromosome 7 copy numbers and losses on chromosome 10 (+7/−10), telomerase reverse transcriptase (TERT) promoter mutations, phosphatase and tensin homolog (PTEN) mutations, homozygous deletions of Cyclin-Dependent Kinases (CDKN2A/CDKN2B), TP53 mutations, NF1

mutations, and less frequent mutations in the phosphatidylinositol …

Standard of care treatment (FDA approved)

Standard care therapy generally relies on three parameters: extended progression-free survival (PFS), enhanced overall survival (OS), and improved symptom control and quality of life [77]. According to the Society of Neuro-Oncology (SNO) and The American Society of Clinical Oncology (ASCO), the primary treatment for patients with IDH-wildtype GBM is safe surgical abscission of the tumor followed by the use of a combination approach comprising radiotherapy (RT) and temozolomide (TMZ, first-line …

Clinical limitations of treatment

The poor prognosis of GBM is attributed to several distinct treatment challenges, including intertumoral and intratumoral genetic diversity, which promotes the emergence of resistant cell subpopulations [105]. Additionally, the tumor's fortified location (barricaded by BBB) impedes effective drug delivery, and the tumor induces intense local immunosuppression, further complicating treatment efforts [106]. For the last four decades, only TMZ has been the first-line treatment; however, MGMT …

Immunotherapy

Immunotherapy acts by reprogramming and utilizing the patient's immune system to fight tumors by causing immunogenic cell death, mainly through autophagy, necrosis, or apoptosis [[129], [130], [131]]. Modern immunotherapy strategies in cancer treatment are primarily centered around immune checkpoint blockade (ICB) agents. Additionally, therapeutics like vaccines, chimeric antigen receptor T cell (CAR-T) therapy, and oncolytic viral therapies have become crucial elements of the current …

Future perspective

Despite the use of an aggressive multimodality approach for GBM treatment composed of surgical resection, chemotherapy, and radiotherapy, GBM continues to have a poor prognosis. Notably, significantly improved survival outcomes in GBM have not been attained with most of the agents and approaches explored, except TT fields, and tumor recurrence has often been evidenced in GBM. The existence of a highly tumorigenic population of cells known as glioma stem cells has been pinpointed as the …

Conclusion

Driven by multiple genetic and epigenetic variations, GBM cells pose a galactic challenge to the researchers who are striving hard to accomplish the pursuit of developing targeted therapies for this highly aggressive and heterogeneous class of cancer. A plethora of studies highlight the

notoriety of GBM cells in the context of their ability to communicate with and manipulate surrounding cells, thereby promoting tumor progression and resistance to developed treatment modalities. GBM cells …

CRediT authorship contribution statement

Mandeep Rana: Writing – original draft, Data curation. **Ke-Chi Liou:** Writing – original draft, Data curation. **Amandeep Thakur:** Writing – original draft, Data curation. **Kunal Nepali:** Writing – review & editing, Writing – original draft, Validation. **Jing-Ping Liou:** Writing – review & editing, Supervision, Resources. …

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. …

Acknowledgment

The corresponding authors are supported by grants from the National Science and Technology Council of Taiwan (grant no. 113-2113-M-038 -003 –,112-2320-B-038-030- and 113-2320-B-038 -055 -MY3). …

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This article is part of a special issue entitled: Cancer Neuroscience published in Cancer Letters.

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