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Advanced nanomicelles for targeted glioblastoma multiforme therapy

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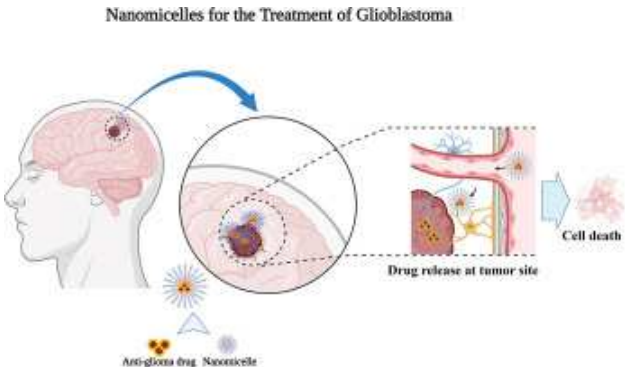
Highlights

- Glioblastoma multiforme (GBM) is a highly aggressive and malignant grade IV brain tumor.
- Nanomicelles hold significant potential for advancing GBM therapy.
- The nanoscale, self-assembling nature of nanomicelles enhances drug bioavailability and stability.
- This review discusses the properties, synthesis strategies, and applications of nanomicelles in cancer therapy.
- Recent advancements in the use of nanomicelles for GBM treatment are summarized.

Abstract

Glioblastoma multiforme (GBM) is the most aggressive and malignant primary brain tumor, classified as grade IV by the WHO. Despite standard treatments like surgical resection, radiotherapy and chemotherapy (i.e. temozolomide), GBM's prognosis remains poor due to its heterogeneity, recurrence and the impermeability of the blood-brain barrier (BBB). The exact cause of GBM is unclear with potential factors including genetic predisposition and ionizing radiation. Innovative approaches such as nanomicelles-nanoscale, self-assembled structures made from lipids and amphiphilic polymers show promise for GBM therapy. These nanocarriers enhance drug solubility and stability, enabling targeted delivery of therapeutic agents across the BBB. This review explores the synthesis strategies, characterization and applications of nanomicelles in GBM treatment. Nanomicelles improve the delivery of both hydrophobic and hydrophilic drugs and provide non-invasive delivery options. By offering site-specific targeting, biocompatibility, and stability, nanomicelles can potentially overcome the limitations of current GBM therapies. This review highlights recent advancements in the use of nanomicelles for delivering therapeutic agents and nucleic acids addressing the critical need for advanced treatments to improve GBM patient outcomes.

Graphical abstract



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Biomedical applications of nanomicelles in GBM therapy

Introduction

Glioblastoma multiforme (GBM) is the most prevalent and aggressive malignant primary tumor of the central nervous system (CNS). GBM is characterized by genetic aberrations, hypoxic microenvironments, necrosis, extensive neoangiogenesis, and poor prognosis, with a 5-year survival rate of <10%. Globally, approximately 3.19 per 100,000 individuals are diagnosed with malignant brain tumors annually, with a higher incidence observed in men [1]. The World Health Organization (WHO) regards it as a grade IV glioma, which is identified by the incidence of necrosis, rapid proliferation, infiltrating tumor growth, and microvascular proliferation. Adult

glioblastomas are one of the most malignant, rare, and deadliest forms, with poor prognosis and lower survival rates [2,3]. The exact cause is unknown; however, researchers speculate that the causes might be one of the following: family history of glioblastoma, exposure to ionizing radiation, viral agents, and germline predisposition [2]. Being an aggressive form of malignant tumor, GBM poses a higher social burden due to its poor prognosis, extensive heterogeneity, recurrence, and significant micromobility [4,5]. Moreover, O^6-methylguanine DNA methyltransferase (MGMT) promoter hypermethylation is a predictive biomarker of a patient's response to the chemotherapeutic agent temozolomide (TMZ) (a DNA-alkylating agent), it cannot be considered the sole defining characteristic of GBM [6]. As a result, no universal treatment approach is effective for all patients. This heterogeneity is a key factor contributing to tumor progression and recurrence of GBM, even in patients who undergo standard care, which typically includes maximal surgical resection followed by radiotherapy with concomitant and maintenance TMZ therapy [7].

Based on the clinical presentation, GBM is classified into primary and secondary glioblastomas. Secondary glioblastomas, which account for approximately 5% of the GBMs, predominantly occur in younger patients, while primary GBMs are more commonly observed in older individuals, typically between 45 and 60years of age. Distinct genetic alterations are observed in primary and secondary GBMs. TP53 (Tumor protein 53) mutations are more frequently associated with secondary GBMs, whereas PTEN (Phosphate and Tensin homologs) mutations and EGFR (Epidermal growth factor receptor) mutations are commonly linked to primary GBMs. However, these patterns are not consistently observed, posing challenges to researchers working towards effective GBM treatments [8]. Patients have clinical presentations of seizures, headaches, focal neurologic deficits, loss of memory, and personality changes [9]. A multimodal therapeutic approach is essential to address the heterogeneity of GBM and improve treatment outcomes, aiming to prolong median and overall survival [10]. However, current standard treatments including radiotherapy, chemotherapy, and maximal surgical resection, have not achieved significant outcomes in curing the disease or elongating the patient's survival. The limited efficacy of these approaches is attributed to several factors including the impermeability of the blood-brain-barrier (BBB), the presence of efflux pumps on the BBB's luminal side, toxicity of the chemotherapeutic agents to normal cells, resistance to chemotherapy, the advanced age of many patients, genetic variability among GBM patients and the challenges associated with early diagnosis.

Personalized and targeted therapeutic approaches capable of crossing the BBB and specifically targeting tumors have emerged as a prominent area of research. This review focuses on nanotechnology-based approaches, particularly the use of nanomicelles, highlighting their synthesis, characterization, and applications fin GBM treatment. Nanomicelles are nanoscale, self-assembled structures with the unique ability to traverse the BBB. They can be synthesized from various biopolymeric components including lipids and amphiphilic polymers, which self-assemble in suitable environment (aqueous or polar, depending on the component). The surface properties of nanomicelles are crucial for enhancing their bioavailability, stability, and interaction with the target tumor tissues [11].

The small size of nanocarriers makes them highly suitable for delivering hydrophobic drugs and

their topical administration, enabling non-intrusive drug delivery even to the posterior eye disorders like age-related macular degeneration and to the brain tumor regions that require nanocarrier to cross the BBB to achieve maximum therapeutic efficiency [12]. Given the limited water solubility of many drugs, novel drug delivery systems that address this challenge have gained significant attention. Nano-micellar delivery systems encompassing drug-polymer conjugates, polymers with low critical micellar concentrations and stimuli-responsive polymers are effectively utilized to enhance the solubility and delivery efficiency of poorly soluble drugs [13].

This review summarizes the conventional treatments for GBM, their limitations, and the potential of nanomicelles as an advanced therapeutic approach. It highlights examples of nanomicelles designed to deliver therapeutic agents and nucleic acids, while also emphasizing their site-specific targeting capability, biocompatibility and stability during administration.

Section snippets

Glioblastoma — an overview

GBM is one of the most aggressive forms of primary brain tumors, predominantly affecting adults, especially males [14]. Classified as a grade 4 astrocytoma, it is the most malignant and disruptive form of brain tumor. Due to the tumor's incurable nature and considerable neurologic morbidity, it imposes a notable socio-economic and medical burden [15]. Despite the availability of advanced diagnostic modalities and ideal multidisciplinary treatments like surgical resection and radiotherapy, along …

Nanomicelles: modern solution for GBM treatment

The potential to create nanoparticles for various applications, such as medication delivery, bioimaging, and diagnosis, has made nanotechnology an exciting field for scientists in the twenty-first century. These nanoscale-sized particles' physical, chemical, and biological characteristics can be altered, opening a world of vast possibilities for improving human well-being through healthcare [51]. Many developments in recent years have rendered these nanocarriers a promising drug delivery …

Applications of nanomicelles in GBM therapy

Nanomicelles are emerging as a promising, cutting-edge solution in the realm of GBM treatment compared to conventional treatment techniques. Due to their nanoscale size, biocompatibility, and stability, they are considered great candidates for delivering therapeutic agents and genes for various malignancy treatments, notably in GBM therapy. The BBB remains in the infiltrative tumor zone due to tumor growth and angiogenesis, making it immune to surgical excision and primarily causing brain …

Challenges and future perspectives

Nanomicelles have proved to be a promising approach for efficient drug delivery and tumor targeting in GBM therapy. Nonetheless, these nanocarriers also have significant hurdles and challenges that limit their applications. Despite the small size of the nanomicelles and leaky vasculature of the tumor microenvironment, systemic administration of these nanomicelles does not ensure the accumulation of the therapeutic agents in a significant toxic dosage. Furthermore, significant genetic …

Conclusion

GBM is an aggressive tumor that requires advanced diagnostic and treatment approaches. In this review, we explored the risk factors, symptoms, classification, and conventional treatment options for GBM. Research evidence has proven that nanomicelles can transport across BBB, selectively target tumor cells, and provide sustained drug release in the tumor microenvironment, resulting in excellent therapeutic outcomes while reducing adverse toxic effects. Furthermore, functionalizing nanomicelles …

CRediT authorship contribution statement

P. Chithra: Writing – original draft, Software, Methodology, Investigation. **Dhiraj Bhatia:** Writing – review & editing, Validation, Supervision, Resources, Formal analysis. **Raghu Solanki:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization. …

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. …

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