



Current perspectives on glioblastoma treatment synergies between therapies and delivery systems

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Abstract

In adults, glioblastoma multiforme (GBM) is considered the most widespread and virulent malignancy of the central nervous system (CNS). This formidable brain tumor stands out as one of the most lethal types within the CNS cancer classification. Despite ongoing advancements in modality therapy, a curative solution remains largely unattainable. Consequently, the imperative to develop innovative systems, plans, and treatment strategies for expanding the repertoire of efficacious agents targeting GBM has emerged as a critical research priority. Presently, oncological research mostly concentrates on enhancing the treatment of glioblastoma multiforme using various innovative drug delivery technologies. Multiple therapies are available at diagnosis, including radiation therapy. New therapeutics are emerging due to breakthroughs in understanding the molecular pathophysiology of GBM and associated cell signaling networks. This comprehensive review examines cutting-edge drug delivery systems and therapeutic approaches for the management of GBM. The innovative methodologies and treatment strategies discussed demonstrate enhanced accuracy, favorable safety profiles, and encouraging effectiveness, potentially paving the way for a revolutionary approach to GBM elimination.

Key words glioblastoma multiforme, delivery systems, central nervous system, stem cell, blood brain barrier

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Introduction

Primary brain tumors, commonly referred to as gliomas, are classified based on their presumed cellular origin. This classification system encompasses several types: astrocytic tumors (which comprise astrocytoma, anaplastic astrocytoma, and glioblastoma), ependymomas, oligodendrogliomas, and mixed gliomas [1, 2]. In the domain of central nervous system (CNS) oncology, gliomas have emerged as the most common malignancies, accounting for approximately 80% of all primary malignant tumors affecting the brain [3].

Glioblastoma multiformes (GBMs) are the most aggressive variant of glioma and a common malignant primary cerebral neoplasm, exhibiting an annual occurrence rate of 3.19 cases per 100,000 individuals in the general populace [4]. Glioblastoma prognosis remains grim, with only 4–5% of patients achieving five-year survival [5]. Notably, short-term outcomes are marginally more favorable, as 26–33% of individuals with this malignancy survive for up to two years following diagnosis [6]. Traditionally, GBMs have been associated with the brain [7]. However, current research has expanded our understanding, revealing that these malignant tumors may manifest in the brainstem, cerebellar regions, and spinal cord [8]. An analysis of the primary glioma distribution revealed that 61% of these neoplasms manifest within the four principal lobes of the cerebrum. The frontal lobe exhibited the highest incidence (25 %), while the temporal lobe accounted for 20% of the cases. The parietal and occipital lobes demonstrate lower frequencies, with 13% and 3% occurrences, respectively [9].

Gliomas are classified by the World Health Organization (WHO) into grades I to IV based on histological criteria that determine malignancy. Lesions with minimal proliferative potential characterize grade I gliomas, which can be effectively treated through curative surgical interventions. Gliomas classified as grades II–IV demonstrate pronounced malignancy and invasive characteristics. GBM distinguishes itself as the tumor variant exhibiting the most invasive behavior, highest degree of malignancy, and least developed cellular differentiation among this group. The WHO has categorized GBM as a grade IV neoplastic entity, reflecting its severe nature [10, 11]. Moreover, glioblastoma has been stratified into four distinct subtypes: proneural, neural, classical, and mesenchymal. Notably, the proneural subtype has a higher incidence among younger patient populations [12, 13]. The most current findings and diverse conclusions regarding GBM treatments must be widely disseminated throughout the scientific, medical, and research communities. As indicated in **Figure 1**, this comprehensive review elucidates and explores a range of cutting-edge drug delivery systems and therapeutic modalities presently utilized in managing GBM.

Epidemiology

The global prevalence of glioblastoma multiforme, although less than 10 per 100,000 individuals, represents a critical public health challenge due to its dismal prognosis and exceptionally low post-diagnosis survival rates [14]. The prevalence of gliomas is most pronounced in the 55–60-year age range, although these tumors constitute approximately 60% of all glioma cases across all age demographics. Malignant gliomas constitute the third most prevalent cause of cancer-related fatalities among individuals aged 15 to 34 years and are responsible for 2.5% of all cancer deaths [15, 16]. Epidemiological data indicate a slightly elevated prevalence of GBM among males relative to females (1.6: 1). Moreover, developed countries exhibit a higher occurrence rate than nations still developing. This disparity may be attributed to inadequate reporting of glioma cases, restricted healthcare accessibility, and divergent diagnostic methodologies in less developed regions [17,

18]. Research has indicated a lower prevalence of GBM among individuals of African descent when compared to other racial groups, including Caucasians, Latinos, and those of Asian heritage [19, 20]. This observed disparity in GBM incidence may be primarily attributed to genetic factors, which are thought to play a significant role in determining the etiology of the disease.

Risk factors

Establishing a definitive correlation between glioblastoma multiforme and environmental or occupational factors remains inconclusive and subject to ongoing investigation. Ionizing radiation is recognized as a significant contributor to glioma formation. Notably, glioblastoma multiforme induced by radiation can manifest long after the initial radiotherapy treatment, which may have been administered for a separate tumor or medical condition [21]. Environmental factors, such as exposure to pesticides, vinyl chloride, synthetic rubber production, and petroleum refining processes, have been preliminarily linked to the development of gliomas [22]. Current scientific evidence has not established a causal link between GBM and mobile phones' electromagnetic fields or nonionizing radiation. Several specific genetic disorders, including retinoblastoma, tuberous sclerosis, neurofibromatosis types 1 and 2, Li–Fraumeni syndrome, and Turcot syndrome, are linked to an increased risk of glioma development [23]. Nevertheless, it is noteworthy that only a small fraction—less than 1% of individuals diagnosed with gliomas demonstrate a known hereditary predisposition.

Clinical presentation

A substantial proportion of patients diagnosed with GBM present with a brief clinical history, typically spanning 3 to 6 months. In contrast, when GBM develops from a low-grade astrocytoma, the clinical timeline often extends over several years [24]. The clinical presentation of a newly diagnosed GBM exhibits significant variability, contingent upon the tumor's dimensions, intracranial position, and the specific cerebral structures affected [25].

The majority of patients typically exhibit headaches, localized or progressive neurologic impairments, and elevated intracranial pressure as their symptoms. Seizures constitute the primary presenting symptom in 25% of patients, with potential recurrence observed in up to 50% of cases during later stages. Notably, approximately 13% of GBM instances may exhibit multifocal (exceeding two lesions), distant (secondary lesion non-contiguous with primary), or diffuse disease manifestations [26]. Advanced imaging techniques, specifically CT or MRI, are typically utilized in the initial diagnostic process for GBM. When using MRI, administering gadolinium contrast significantly enhances the visualization of most GBMs. These tumors characteristically manifest as irregularly contoured masses, exhibiting a dense enhancement ring surrounding a hypointense necrotic core [27]. The WHO grading system identifies necrosis as a critical component in diagnosing GBM. This distinctive feature is necessary for classifying a brain tumor as grade IV or GBM [28]. Additionally, diagnostic imaging may reveal the presence of peripheral vasogenic edema, hemorrhagic regions, and distortions in ventricular structure.

Pathogenesis

GBM exhibits a marked predilection for the cerebral hemispheres, with 95% of cases arising in the supratentorial region. In contrast, the incidence of GBM in the brain stem, cerebellum, and spinal cord is substantially lower, accounting for a small fraction of all reported instances [29]. The macroscopic presentation of GBM

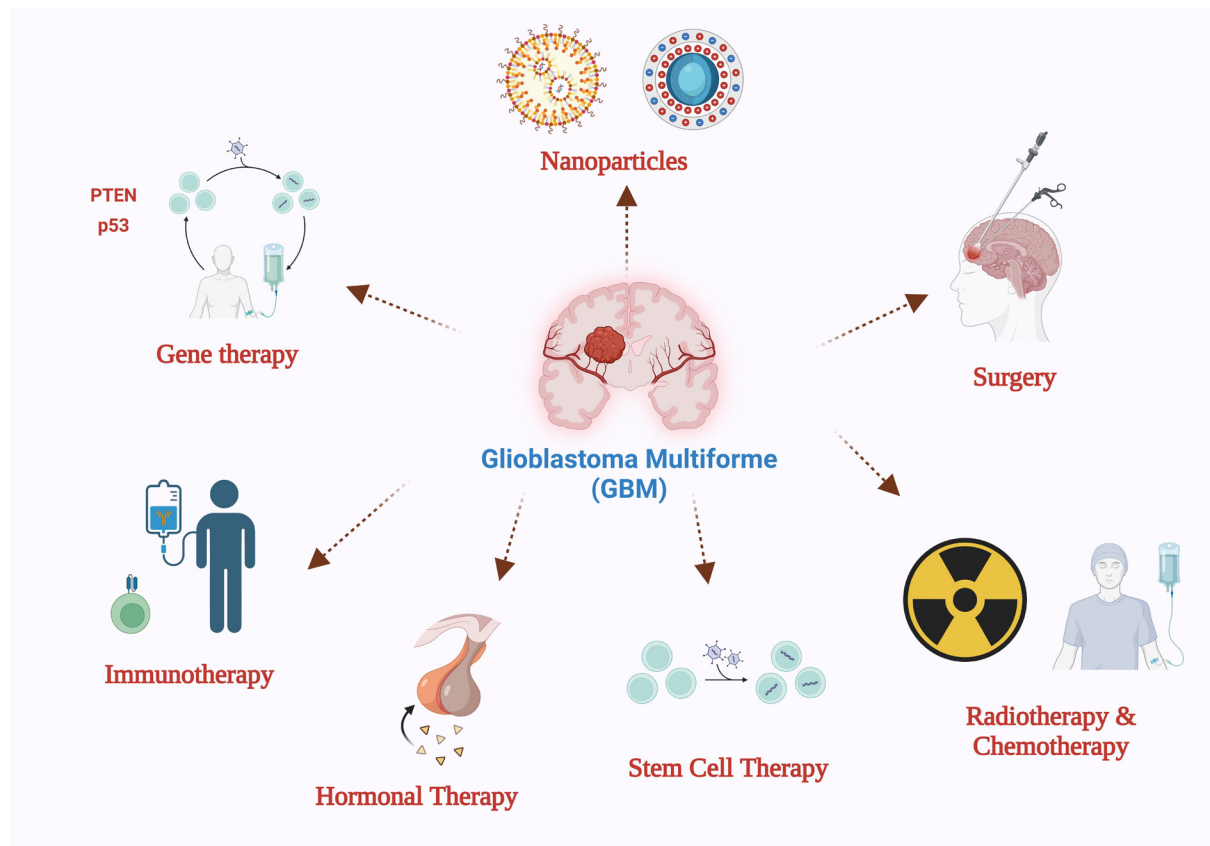


Figure 1. Glioblastoma multiforme (GBM) means of delivery and treatment options.

is notably diverse, with prominent features including areas of necrosis, multiple sites of hemorrhage, and regions exhibiting cystic and gelatinous characteristics. A hallmark characteristic of GBM is the diverse macroscopic presentation of the tumor across various regions. Necrotic areas manifest as soft, yellow-hued tissue, while other sections of the cancer exhibit a firm, white appearance [30]. Furthermore, certain regions display pronounced cystic degeneration and hemorrhagic features.

The neoplastic growth typically presents as an isolated, comparatively sizable, and irregularly contoured lesion that predominantly originates in the white matter. From a histological perspective, GBM shares characteristics with anaplastic astrocytoma, exhibiting a pleomorphic cellular composition that spans from small, poorly differentiated neoplastic elements to large, multinucleated cells. This presentation is accompanied by multifocal necrosis featuring pseudo-palisading nuclei and a high degree of mitotic activity [30, 31]. Vascular endothelial cell proliferation forming glomeruloid structures constitutes a significant defining feature.

GBM is classifiable into two forms: primary (de novo) and secondary. The origin of primary GBM is not linked to a known precursor, whereas secondary GBM evolves from the progression of a lower-grade glioma. The preponderance of GBM cases is classified as primary, with affected patients typically being older and demonstrating a less favorable clinical outcome in comparison to those diagnosed with secondary GBM [32]. The genetic pathogenesis of GBM follows two distinct routes. Primary glioblastoma results from the immediate conversion of glioma precursor cells, characteristically linking simultaneous modifications in multiple genes, notably EGFR and VEGFR.

In contrast, secondary glioblastoma emerges through a gradual sequence of pathological alterations, with each stage linked to specific genetic modifications, including those affecting p53, CDK4, and P13K, among other genes [33].

GBM conventional treatment and resistance

Surgical resection

During the late 1980s and early 1990s, the advent of frameless stereotaxy represented a significant turning point in brain tumor surgery. This innovative technique enabled surgeons to maneuver and place instruments precisely through image-guided systems. With the advancement of imaging technologies, frameless stereotaxy has evolved, enhancing the precision of surgical interventions for brain tumors [34]. Cerebral cortical stimulation has emerged as a crucial technique for intraoperative identification of eloquent brain regions that must be preserved during surgical procedures. This methodology, known as "brain mapping," enables surgeons to account for individual anatomical variations and potential tissue reorganization. By employing this approach, medical professionals can effectively excise tumors in areas of high functional significance while reducing the danger of compromising the patient's quality of life [35, 36].

The importance of imaging methodologies has grown substantially in GBM surgical procedures [37]. These imaging modalities serve to guide biopsy procedures, delineate tumor margins, and precisely localize critical brain structures that require preservation [38-40]. MRI emerges as the optimal technique for brain tumor imaging, offering unparalleled detail in anatomical

structures and differentiation of soft tissues, which exceeds the capabilities of CT scanning and is useful for emergent imaging. Various MRI contrasts and pulse sequences can highlight critical tumor and brain tissue features, such as blood vessels, tumor necrosis, and hemorrhage (contrast-enhanced T1-weighted), cerebrospinal fluid (T2-weighted), and blood perfusion (dynamic susceptibility contrast (DSC), dynamic contrast-enhanced (DCE) and arterial spin labeling (ASL) [41, 42].

Intraoperative magnetic resonance imaging (iMRI) and intraoperative ultrasound (iUS) are valuable tools for neurosurgeons to detect residual malignant tissue during surgical interventions. Following the initial tumor excision, the surgeon conducts a contrast-enhanced MRI examination within the operating suite using specialized intraoperative imaging equipment. Should any residual enhancing tissue be observed, the surgeon proceeds to remove this additional tissue during the same operative session [43, 44].

Chemotherapy

The established post-operative therapeutic approach involves a 6-week course of simultaneous TMZ administration (75 mg/m²) and radiotherapy, succeeded by an adjuvant TMZ regimen (150–200 mg/m²) delivered for six cycles. The treatment was administered across five successive days, with each cycle separated by a 28-day interval [45]. Temozolomide (TMZ), a small-molecule alkylating agent, is the primary chemotherapeutic drug for GBM. This compound exerts its antitumor effects by directly inducing DNA damage through the methylation of purine bases [46, 47].

The formation of O6-methylguanine lesions constitutes the principal cytotoxic action, resulting in the initiation of apoptosis, autophagy, and cell degeneration. Furthermore, investigations have demonstrated that TMZ exhibits radiation-sensitizing effects. The concurrent administration of this agent with radiation therapy amplifies the potential for radiation-induced double-strand breaks in DNA, thereby increasing the likelihood of cellular demise [48, 49].

The exploration of nitrosourea-based compounds has been a significant avenue in GBM treatment research. One such agent, Carmustine, is characterized as a compact nitrogen mustard molecule that functions as an alkylating agent. Its action mechanism involves interstrand cross-links between guanine and cytosine nucleobases within the DNA structure [50, 51]. The therapeutic alkylating effects of Carmustine can be counteracted by the alkyl guanine transferase (AGT) enzyme. Consequently, Carmustine is often administered with AGT inhibitors to ensure optimal therapeutic efficacy. Lomustine, a member of the alkylating antitumor agent class, exhibits exceptional characteristics that set it apart from its counterparts. The compound's notable lipophilicity and compact molecular structure enable its efficient penetration of the blood brain barrier (BBB). These distinctive features contribute to lomustine's suitability for oral administration, enhancing its therapeutic potential in oncology [52].

The anti-angiogenic properties of bevacizumab, a humanized monoclonal antibody, are utilized through its intravenous administration. This therapeutic agent functions by connecting to and inhibiting vascular endothelial growth factor A (VEGF-A), a

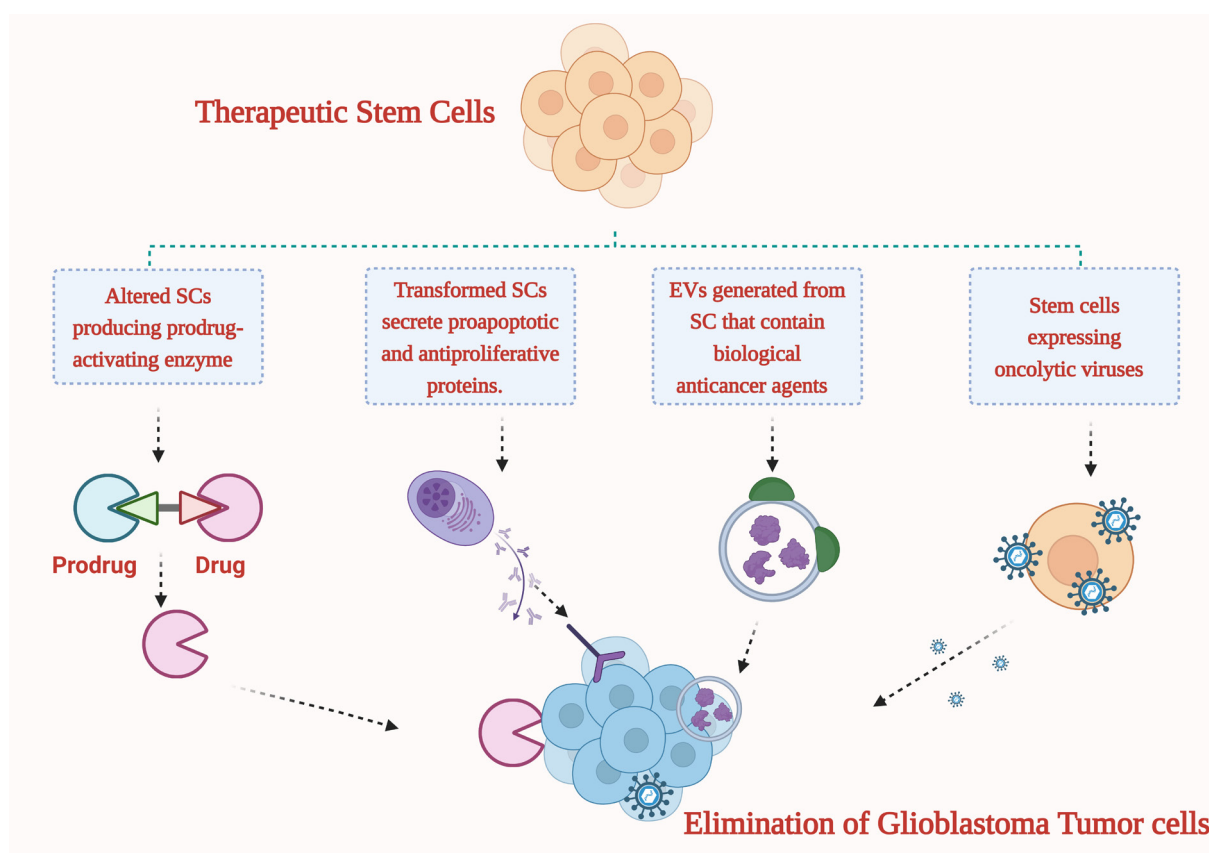


Figure 2. Methods for combating glioblastoma with the help of modified stem cells (SCs) and the extracellular vesicles generated by SCs that express and transport various drugs.

protein that, when bound to its receptor, triggers the development of fresh blood vessels [53, 54]. Bevacizumab exhibits a notable impact on progression-free survival in glioblastoma patients; however, it does not confer a substantial benefit in terms of overall survival for those newly diagnosed with this malignancy. Consequently, its primary utilization is focused on the treatment of recurrent glioblastoma cases [55].

Radiation therapy

Radiation therapy encompasses multiple modalities, such as x-ray photons, gamma photons, and protons; however, not all of these approaches have been substantiated as conventional therapeutic interventions. It can facilitate local control of the microscopic illness not addressed by surgical ablation. In CCRT, patients undergo 3D conforming radiotherapy, utilizing X-ray photons aimed at the tumor from many orientations. CT and MRI scans are employed to strategize administering the therapeutic dose to the tumor location. The standard protocol for radiation therapy involves the administration of 2 gray (Gy) fractions over a 6-week course, with cumulative doses ranging from 40 to 60 Gy [56]. In 80–90% of cases, recurrent gliomas typically emerge within a 2 cm radius of the initial tumor site, leading to the clinical adoption of conformal radiotherapy as the preferred treatment modality over whole-brain radiation [57]. Conformal radiotherapy is engineered to precisely target most residual GBM cells, simultaneously preserving the integrity of healthy cerebral tissue and minimizing cognitive adverse effects.

Stereotactic radiosurgery (SRS) represents an additional modality of focal radiation treatment, allowing for the application of significantly elevated radiation doses [58]. This is achieved through the utilization of multiple converging radiation beams that are non-parallel. The radiation protocol employed in SRS is characterized by administering higher doses per fraction, typically exceeding 15 Gy and a reduced number of fractions [59]. The method employs a cobalt-60 source to generate gamma radiation, accurately focused on the tumor using custom-designed beam shapers. SRS has gained widespread acceptance in treating brain metastasis, primarily due to its ability to reduce the cognitive complications associated with whole-brain radiotherapy. In certain instances of GBM, SRS might be considered an appropriate treatment approach [60].

Innovative methods for drug delivery

Researchers have employed various innovative drug delivery systems to treat multiple cancer types. Additionally, numerous studies have provided contemporary insights and advancements in novel drug delivery methods for diverse cancers and other life-threatening illnesses. Given the prevalence of GBM among CNS gliomas, there exists an urgent requirement to explore innovative drug delivery mechanisms specifically tailored for GBM treatment [61]. Nanoparticles (NPs) exhibit versatile applications in gene therapy, diagnostic procedures, therapeutic interventions, and medical imaging. Among the crucial attributes of NPs, surface charge plays a significant role. Experimental evidence suggests that neutral NPs and low concentrations of anionic NPs do not compromise the integrity of the BBB. However, elevated levels of anionic NPs, as well as cationic NPs, have been observed to affect the BBB's structural integrity adversely [62, 63].

NPs demonstrate the capacity to diminish the effectiveness of certain active pharmaceutical ingredients. These microscopic structures serve as protective agents, shielding medications from enzymatic and chemical degradation. Additionally, NPs can facilitate targeted delivery of various active compounds, including cytostatic agents, antitoxins, proteins, nucleic acids,

and polypeptides, to specific tissues. Additionally, the versatility of NPs allows for their administration through diverse routes, encompassing oral, percutaneous, intra-ophthalmic, intranasal, and intravascular pathways [64].

Novel theranostic nanocarriers provide real-time imaging and treatment of diseases. The development of theranostic agents remains challenging. A multifunctional theranostic nano system based on dendrimers was developed for malignant tumor cell chemotherapy and CT imaging, emphasising specification [65]. The synthesis of a fifth-generation (G5) polyamidoamine (PAMAM) dendrimer incorporated doxorubicin (DOX), an exemplary antineoplastic agent, through an acid-labile cis-aconityl (NHAc) bond. The dendrimer was further modified by prefunctionalization with folic acid (FA) to yield the final G5 construct. Gold nanoparticles (Au NPs) were also employed to encapsulate NHAc-FA-DOX conjugated mixtures, forming Au NP dendrimers (Au DENPs). The DOX-conjugated Au DENPs demonstrates promising potential for simultaneous implementation in chemotherapeutic treatment and CT imaging across various classifications of malignant neoplasms [66].

The effectiveness of anticancer medications in GBM treatment is hampered by three primary factors: increased systemic toxicity, inadequate cancer cell-specific targeting, and suboptimal penetration of the BBB. In response to these constraints, researchers have turned to solid lipid nanoparticles (SLNPs) as a possible solution. These nanoparticles demonstrate enhanced biocompatibility and reduced systemic toxicity compared to conventional drug delivery approaches and other anticancer agents currently used for GBM treatment. The outermost portion of solid lipid nanoparticles was conjugated with lipoprotein receptor-related protein 1 (LRP1) and angiopep-2, a ligand found in the epithelial cells of both the brain and glioma, for the delivery of docetaxel (DTX). The Angiopep-2 linked solid lipid nanoparticles (A-SLN) demonstrated enhanced cytotoxicity, superior cellular uptake, and encouraging apoptosis relative to the blank (unconjugated SLNPs) against U87MG human glioblastoma and GL261 murine glioma cells. Furthermore, tissue distribution and pharmacokinetic evaluations demonstrated that A-SLN exhibited enhanced brain-specific targeting and accumulation compared to the commercially available DTX formulation (Taxotere). The findings from these studies suggest that A-SLN could be a valuable therapeutic approach for addressing GBM [67].

Surface characterization studies have revealed the potential of zinc oxide (ZnO) nanoparticles (NPs) as a therapeutic agent in cancer treatment. A particular investigation focused on the relationship between ZnO NPs and three predominant blood proteins: albumin, fibrinogen, and apo-transferrin. These proteins were attached to ZnO NPs through two distinct mechanisms: covalent bonding (c-ZnO NPs) and non-specific adsorption (n-ZnO NPs). The research sought to elucidate how these alternative attachment methods influenced protein structure and their subsequent effects on GBM cells. Fourier-transform infrared spectroscopy (FTIR) examined the protein structures and modification of ZnO NPs. FTIR study showed that noncovalent contact considerably impacted the secondary structure of proteins compared to those covalently bound to ZnO NPs. The experimental findings revealed that albumin-conjugated c-ZnO NPs and apo-transferrin exhibited a dual effect on U373 cells at subtoxic concentrations. These compounds interfered with cellular cycle progression while mitigating the necrotic cell death rate. Such observations suggest potential therapeutic implications for the treatment of GBM cells [68].

Celecoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, demonstrates its therapeutic effects by modulating apoptotic pathways and cellular growth mechanisms [69]. Investigations have revealed that nanoparticles comprising celecoxib-conjugated

poly(lactic-co-glycolic acid) (PLGA) exhibit substantial antineoplastic activity against glioma cell lines, specifically U87MG and C6, with effectiveness correlating to the administered dose. These findings suggest that celecoxib-functionalized PLGA nanoparticles constitute a promising drug delivery system for the management of GBM [70].

Stem cell treatment for GBM

Stem cells play a pivotal role in the genesis and regeneration of tissues throughout the entire lifespan of all living organisms, including humans [71]. Stem cells exhibit the unique self-renewal property, maintaining their proliferative capacity while generating new stem cells and differentiated daughter cells that replenish the functional cell pool. These cells are characterized by their pluripotency, enabling them to produce diverse lineages of daughter cells. Stem cells (SCs) are classified into four distinct categories: two physiological types occurring at different life stages—embryonic SCs (ESCs) and adult SCs (ASCs); one synthesized variety known as induced pluripotent SCs (iPSCs); and a pathological form found in cancer, referred to as cancer stem cells (CSCs). As illustrated in **Figure 2**, stem cells can be altered in multiple manners or loaded with diverse payloads to enhance their anticancer efficacy against glioblastoma.

Emerging research has revealed that glioblastoma harbors a distinct subclass of cells recognized as glioma stem cells (GSCs). These GSCs exhibit remarkable characteristics, including self-renewal potential and heightened proliferative capacity, attributing to the swift onset of tumor infiltration and metastasis [72, 73]. The management of GSCs plays a pivotal role in averting tumor recurrence. Normal SCs migrate toward tumor sites and interact with CSCs, making them valuable tools for targeting GSCs in GB therapy. The interplay between normal SCs and GSCs suppresses tumor proliferation, angiogenesis, and metastasis while diminishing inflammation and apoptosis. Studies have demonstrated that human MSCs and HSCs can specifically target GSCs and impede GB progression [74, 75].

Antiproliferative proteins represent a category of biological agents that impede the association between native ligands and their corresponding receptors. A prime illustration of this mechanism is the obstruction of epidermal growth factor (EGF) attachment to its receptor variant III (EGFRvIII). These characteristics position these proteins as an ideal therapeutic avenue for GB, given their capacity to interfere with essential cellular communication pathways [76]. As a result, a decrease in the growth of cancerous cells was revealed [77, 78]. In antiproliferative agents, a select subset possesses the unique ability to be extruded into the extracellular space. Interferons α (IFN- α) and β (IFN- β) have been shown to influence tumor cell growth in diverse pre-clinical cancer models. A recent investigation evaluated the effects of IFN- β , a representative cytokine expressed by therapeutic SCs, on glioblastoma progression in murine models. The findings demonstrated that systemic administration of this cytokine reduced tumor growth [79].

Bone morphogenetic proteins (BMPs) can impede tumor progression by activating their corresponding receptors (BMPRs). Furthermore, BMP4 secreted by human adipose-derived mesenchymal stem cells demonstrates efficacy in suppressing tumor growth and enhancing the longevity of mice afflicted with glioblastoma [80, 81]. Certain SC proteins, notably growth arrest specific-1 (Gas1), trigger cell cycle arrest and demonstrate antitumoral properties against glioblastoma [82]. SC therapy is emerging as a potentially transformative approach to treating glioblastoma. As extensively discussed, SCs possess an innate ability to home in on tumor sites, making them mainly ideal for the delivery of anticancer agents. To address the challenges of

traditional drug delivery systems (DDSs), often hampered by brief half-lives, both SCs and their secreted extracellular vesicles (EVs) can express or encapsulate various antitumor payloads. Moreover, SCs demonstrate potential in detecting brain tumor masses, enhancing their value in glioblastoma management.

Conclusion

The primary objective of every anticancer therapy is to reduce cancer cell proliferation while effectively ensuring maximum safety. Cancer research predominantly emphasizes the management of GBM by various nano-systems and medicines addressed in the present review. These delivery systems and therapeutic strategies have emerged with significant attention as prospective alternatives for addressing the previously encountered obstacles in effectively targeting multiple cancer cells, demonstrating numerous promising characteristics. These diverse innovative drug delivery methods and therapeutic approaches are precise, harmless, and relatively efficacious. As a result, they may pave the way for a novel approach to eradicating GBM.

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Ethics approval

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Data availability

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Authors' contribution

DD contributed to the conception, design, writing of this review article, figures drawing and submitted the final version of the manuscript.

Competing interests

None.

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