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Review

Modern insights of nanotheranostics in the glioblastoma: An updated review

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Highlights

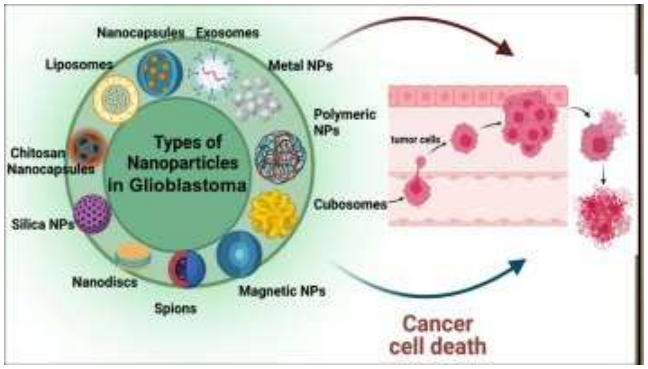
- Exosomes in nanotechnology are highly indispensable for the effective glioblastoma multiforme (GBM) therapy.
- Exosomes derived from specific cell types can transport endogenous signaling molecules useful for GBM.
- Cell membrane-camouflaged nanoparticles (CMCNPs) are promising theranostic agents for targeting GBM cells.
- This review contributes recent insights of valuable divergent nanotheranostics for the GBM.

Abstract

Glioblastoma multiforme (GBM) is a highly malignant subtype of glioma, originating from the glial cells that provide support to other neurons in the brain. GBM predominantly impacts the cerebral hemisphere of the brain, with minimal effects on the cerebellum, brain stem, or spinal cord. Individuals diagnosed with GBM commonly encounter a range of symptoms, starting from auditory abnormalities to seizures. Recently, cell membrane-camouflaged nanoparticles

(CMCNPs) are evolving as promising theranostic agents that can carry specific biological moieties from their biological origin and effectively target GBM cells. Moreover, exosomes have gained widespread scientific attention as an effective drug delivery approach due to their excellent stability in the bloodstream, high biocompatibility, low immune response, and inherent targeting capabilities. Exosomes derived from specific cell types can transport endogenous signaling molecules that have therapeutic promise for GBM therapy. In this context, researchers are utilizing various techniques to isolate exosomes from liquid biomarkers from patients, such as serum and cerebrospinal fluid (CSF). Proper isolation of exosomes may induce the clinical diagnosis in GBM due to their commercial accessibility and real-time monitoring options. Since exosomes are unable to penetrate the blood-brain barrier (BBB), strategic theranostic methods are ideal. For this, understanding interactions between glioma-specific exosomes in the TME and biomarkers is necessary. The versatile characteristics of NPs and their capacity to cross the BBB enable them to be indispensable against GBM. In this review article, we discussed the recent theranostic applications of nanotechnology by comparing the limitations of existing nanotechnology-based approaches.

Graphical abstract



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Introduction

Based on their degree of malignancy, gliomas fall into four grades (WHO I, II, III, and IV), with type IV glioma, also known as glioblastoma (GBM), being the most fatal. Patients' survival rate and percentage curability are very low [1]. Although the etiology of GBM remains uncertain, it may be associated with ionizing radiation, smoking, dietary risk, or head injuries. GBM mostly affects the cerebral hemisphere, with a few cerebellar, brain stem, and spinal cord tumors. GBM patients include hearing and visual problems, increased intracranial pressure, and convulsions in 40% of cases [2]. According to the 2020 CBTRUS Statistical Report, the prevalence of GBM is increasing annually, with an incidence rate of 3.22 per 100,000 cases and a 5-year survival rate of 7.2% [3,4]. GBM is associated with numerous genes, including those on chromosomes 7 and 10, tensin homolog tumor suppressor genes, cyclin-dependent kinase inhibitors 2A and B, and the

promoters of telomerase reverse transcriptase (TERT). In 70% to 80% of early GBMs, TERT promotor mutations decide how long the telomeric DNA is. These mutations are necessary for GBMs to become immortal and grow. About 40% of initial GBMs had EGFR gene amplification, which increased tumorigenicity, cell proliferation, and apoptosis resistance. Secondary GBM spread more quickly when there were IDH1/2 mutations, more P53 proteins in the tumor, and X-linked thalassemia or mental retardation. Mutations in IDH1/2 are crucial for distinguishing secondary GBM from main GBM. Whether tumor-targeted treatment can correct IDH1/2 mutations is uncertain [5]. Secondary glioblastomas are thought to develop from a lower-grade glioma that advances or changes. Primary GBM has no recognized clinical antecedent [6,7]. The 2016 and 2021 WHO classifications and guidelines form the third category [8,9]. 70–80% of low-grade gliomas, 5–10% of main GBM, and secondary GBM show IDH1 and IDH2 mutations. This allows us to further subcategorize GBM into three groups: IDH-wild type (giant cell, gliosarcoma, epithelioid), IDH-mutant, and not otherwise described. Numerous standard approaches diagnose GBM. MRS, fMRI, and biopsy are therapeutically essential (Fig. 1). Palliative care usually becomes necessary after diagnosis due to limited options and poor quality of life. Since peptide-based delivery techniques may have off-target effects, we require a new early detection and noninvasive treatment strategy.

Over the past decade, “all-in-one” theranostic nanoplatforms that integrate diagnosis and therapeutics have improved brain cancer care. These include MRI/CT imaging before surgery, radiation therapy (RT), and chemotherapy after surgery. Their key benefits include sensitive early-stage tumor identification, real-time surgical planning and intraoperative surgery guidance, nanomedicine administration, PK/PD monitoring, and therapeutic treatment feedback monitoring. Photothermal and photodynamic therapies (PTT and PDT) are possible with several NIR nanoprobes. Laser irradiation induces nanoprobes to FLI or PAI, causing PTT hyperthermia or PDT ROS. Even though it is minimally invasive, very effective, simple to use, and has led to amazing advances, single-mode PTT or PDT cannot cure cancers because they are complex, varied, and heterogeneous [10]. Using photosensitive NPs along with non-invasive NIR irradiation is a more comprehensive way to treat diseases than traditional methods. The therapy platform achieves a high level of spatial and temporal treatment accuracy for aggressive and deeply seated GBM tumors, and this, in turn, makes NIR-based therapies safer. It's important to note that RGD-K peptides can specifically target αvβ3 integrin receptors, and ALTS1C1 GBM cancer cells overexpress these receptors. For these reasons, researchers designed EuB6@RGD-K NPs through the surface modification of europium hexaboride (EuB6) NPs with the RGD-K peptide, which facilitated the strong adherence with these GBM cancer cells. EuB6@RGD-K NPs significantly target GBM cells by exerting their potential nanotheranostic effects under NIR-II (1064nm) and NIR-III (1550nm) light irradiations. EuB6@RGD-K NPs deliver exceptional photostability and a photothermal conversion efficiency (η) of 39.2% under NIR-III (1550nm) light irradiation. In addition, EuB6@RGD-K NPs can form abundant singlet O_2 through NIR-II 1064nm photoexcitation and further generate excess hydroxyl radicals through NIR-III 1550nm light irradiation. These EuB6@RGD-K NPs can facilitate combined PDT and PTT effects at NIR-II (1064nm) and NIR-III (1550nm) wavelengths to destroy cancer cells in both in vitro and in vivo models [11].

Bangham et al. produced liposomes, vesicles containing an aqueous core and concentric phospholipid bilayers, in 1965 [12]. Liposomes have become popular for improving tumor-site specificity, therapeutic effectiveness, and encapsulating medication toxicity. The key reasons include biocompatibility, longer plasma circulation duration, prolonged biological half-life, biodegradability, and low immunogenicity. GBM treatment is intriguing for its use of lipid carriers as theranostic agents in gene delivery methods [[13], [14], [15], [16]] Akbarzadeh and colleagues categorized liposomes as MLV, LUV, and SUV [17]. Unfortunately, traditional liposomes are unstable, short-lived, and rapidly release drugs into the bloodstream. Conventional methods for synthesizing liposomes include hydrating the lipid film using a French pressure cell, membrane extrusion, solvent injection, reverse phase evaporation, freeze-thaw extrusion, micro-emulsification, and removing detergents such as alkyl glycoside, Triton X-100, or cholate from mixed micelles [[18], [19], [20], [21], [22]]. In this regard, active ligand-functionalized liposomes and lipid nanocapsules (LNCs) have recently gained scientific interest for the GBM theranostic applications.

Due to their excellent blood circulation stability, biocompatibility, low immunogenicity, and natural targeting, exosomes are acting as promising nanotheranostic agents. Exosomes transport specific therapeutic components, such as proteins, nucleic acids, and lipids, to their surfaces, facilitating cell communication [23]. Exosome payloads vary by origin and biological state, which are crucial to GBM treatment. Receptor-ligand interactions deliver antigens, allowing exosomes to enter certain cells and fuse membranes to move surface proteins [[24], [25], [26]]. Exosomes' molecular makeup is identical to their CM, which prevents the immune system from picking them up, causing inflammation, or clearing them quickly [[27], [28], [29]]. Previous isolation procedures were tedious, non-commercial, and required extensive tuning, which slowed clinical diagnosis. Researchers can build simple and strategic glioma theranostic techniques by separating exosomes directly from patient blood and CSF for liquid biomarker investigations. We must examine new nanotheranostic-based glioma-specific exosomes.

Recently, nanomaterials have increased BBB permeability for GBM-targeted treatment. Combining therapeutic and diagnostic chemicals in a nanomaterial might provide dual GBM theranostics. The researchers created BBB-transportable NPs smaller than 14nm for GBM theranostics. Researchers use poly(acrylic acid) to stabilize and alter extremely tiny gadolinium oxide NPs using reductive bovine serum albumin. The nanocomplex was biocompatible and could cross the in vitro and mouse BBBs due to its small particle size and structural tailorability. Researchers found ES-GON-rBSA3-LFRGD2 in orthotopic GBM, which means it might be useful as a radiosensitizing agent for treating GBM [30].

For the last decade, researchers have used zero-dimensional nanomaterials like graphene and carbon quantum dots (GQDs and CQDs) in GBM treatment due to their intriguing features. Researchers are exploring strategies to combat GBM that incorporate photophysical, ultra-nanoscale, electrochemical, fluorescence-tunable, and receptor-based targeting properties in PDT, PTT, and selective nanotheranostics. Transferrin-conjugated CQDs can traverse the BBB concentration- and time-dependently. Changes to their surfaces enable CQDs to use glucose transporters and passive diffusion to transport anticancer drugs from the blood to the brain [31].

In recent times, cell membrane-camouflaged nanoparticles (CMCNPs) are becoming more popular among researchers in clinical and theranostic applications because they are superiorly biocompatible and stay in the bloodstream for a long time [32]. Researchers employed cancerous cells, RBC, platelets, and macrophages to prepare hybrid membranes. The fact that CMCNPs can encapsulate biologically produced CMs and deliver specific medications to specific locations reduces off-target accumulation. Therefore, reducing side effects can enhance therapeutic effectiveness against GBM, particularly when CMCNPs carry specific theranostic agents. This review focuses on the recent advancements in various nanomaterials used in nanotheranostics applications for treating GBM. We also discussed various approaches, existing limitations to nanomaterials, and explored future directions in GBM therapy.

Section snippets

Convection enhanced delivery of nanocarriers in GBM therapy

Bobo et al. introduced CED in 1994 [33]. CED may provide a variety of benefits. In contrast to diffusion-limited delivery, CED improves interstitial medication dispersion with pressure. Localized administration reduces neurotoxicity because infused dosages are lower than diffusion-mediated distribution. Compared to implanted polymers, CED may not increase brain damage risk [34]. The CED method in animals and humans has found transitory and reversible neurological effects in the eloquent regions …

Nanotechnology-based approaches for GBM theranostics

Until the advent of nanotechnology, researchers and medical professionals relied on other contemporary approaches: (i) immunotherapy, (ii) genetic engineering, (iii) drug delivery, and (iv) nanomedicine, etc. (Fig. 2). Among these, nanotechnology-based therapy has gained popularity due to its versatility, biocompatibility, cost-effectiveness, etc. Specifically, its non-invasiveness and enhanced surface-to-volume ratio properties make it engaging for its broad applicability in major clinical …

Combinatorial nanomedicines; as therapeutic targets in GBM therapy

Despite much research, there is no effective treatment for GBM. Researchers are actively working toward the development of effective and unique treatment techniques for GBM. So far, the standard treatment for GBM is surgical resection, followed by TMZ-based chemoradiotherapy. However, recurring GBM tumors are a common phenomenon, despite full surgical resection and vigorous adjuvant therapy received. Overall, several factors could complicate the treatment of GBM, such as incomplete resection, …

Limitations and future prospective

Nanomaterials, as a novel type of material with the potential to pass through biological barriers and precisely target tumors, play a vital role in the administration of various medications, opening up new avenues for the development of sophisticated therapeutics for brain tumor therapy. Depending on their size, NP's EPR effect can allow them to enter tumors rather than non-tumorous tissues. Extended nanomaterial circulation can lead to a maximum half-life in the blood, resulting in extended …

Conclusion

GBM is a highly aggressive glioma that scientists and medical professionals are still struggling to treat. Even with conventional care, patients with GBM have a median survival time of 15 months after the initial diagnosis. Until we achieve breakthroughs that can extend the lives of GBM sufferers, it's critical to keep coming up with new ideas. Extensive research is exploring GBM's aggressive behavior. GBM's flaws are also being discovered. The rapid growth of GBM tissue, as evidenced by …

CRediT authorship contribution statement

Roopkumar Sangubotla: Writing – review & editing, Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Kumar Shiva Gubbiyappa:** Writing – review & editing, Writing – original draft. **Rajakumari Devarapogu:** Writing – review & editing, Writing – original draft. **Jongsung Kim:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition. …

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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