Review Article

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Membrane-based biomimetic delivery systems for glioblastoma multiforme therapy

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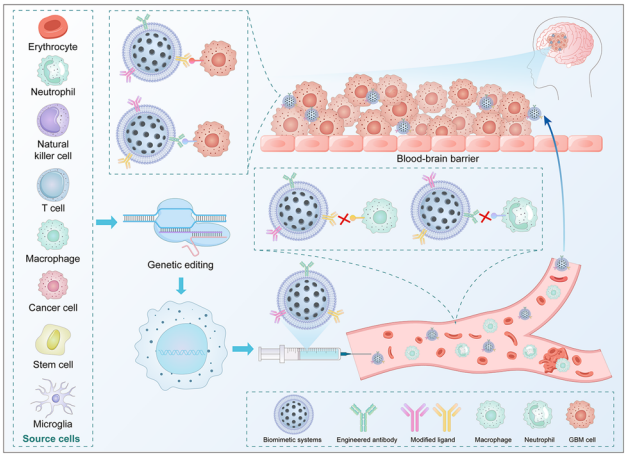
Abstract: Recent breakthroughs in glioblastoma multiforme (GBM) treatment have been driven by nanotherapeutics utilizing cellular membranes. This approach combines the unique properties of cellular membranes with the advantages of nanomaterials, mimicking the physiological functions of natural cells. These biomimetic systems can effectively cross the blood–brain barrier and deliver drugs precisely to the brain, significantly improving targeted drug delivery. This review explores various types of cellular membranes – such as those from red blood cells, immune cells (including natural killer cells, T cells, macrophages, and neutrophils), cancer cells, stem cells, and hybrid cell membranes – that have been used in developing biomimetic systems for GBM treatment. These membranes not only retain the targeting characteristics of their parent cells but can also be enhanced for GBM cell recognition through gene editing or ligand modification. This article also discusses the construction methods for biomimetic nanoparticles and their *in vitro* validation techniques. Finally, the review outlines the challenges of membrane coating and potential strategies for translating these systems into clinical use. It is anticipated that these innovative membrane-coated nanoparticles will provide new therapeutic options for GBM patients.

Keywords: membrane-based, nanomaterials, glioblastoma multiforme, drug delivery, blood–brain barrier



Graphical abstract

1 Introduction

Glioblastoma multiforme (GBM) is one of the most common and aggressive cancers of the central nervous system (CNS), with an extremely poor prognosis for patients [1,2]. Despite comprehensive clinical treatment strategies, including surgery, radiotherapy, and chemotherapy, the median survival time for GBM patients remains less than 15 months, with little improvement over the past decade [3]. This is primarily due to the unclear causes of GBM and the difficulty in effectively delivering drugs to the tumor site across the blood–brain barrier (BBB), a highly selective membrane that separates the circulating blood from the brain's extracellular fluid [4].

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Therefore, developing novel drug delivery carriers that can cross the BBB and target GBM has become a critical need in its treatment.

Biomimetic cell membranes (CMs), a cutting-edge technology in nanomedicine, have sparked significant research interest [5]. The core of this approach involves using naturally occurring biological membranes – such as those from red blood cells (RBCs) (erythrocytes), immune cells, cancer cells, and stem cells – to encapsulate drugs in membrane vesicles for precise delivery (Figure 1). A key advantage of this method is that the antigen structures on the surface of these membranes can help evade recognition by immune cells, reducing the drug's clearance rate and prolonging its circulation time in the body. Additionally, the tightly encapsulated drug delivery system minimizes drug leakage, thus helping to reduce drug toxicity [6]. The abundant functional molecules on the surface of biological membranes, including proteins and glycoproteins, further enhance the ability of these systems to recognize and bind to tumors, improving targeted delivery [7]. Furthermore, technologies like gene editing and peptide modification can further refine the targeting of CMs toward GBM cells (Figure 2). However, because drug toxicity can potentially damage biological membrane systems, researchers have combined CMs with nanocarriers to create novel biomimetic nanodrug delivery systems [8]. This combination leverages the "autologous" properties of biological membranes and the advantages of "artificial" nanocarriers, significantly improving the biocompatibility of the system and reducing immunogenicity. Moreover, these systems greatly extend blood circulation times. By modifying the membrane surface with targeting peptides and other molecules, this approach allows for precise drug delivery to specific tumors like GBM, offering promising new strategies for cancer treatment.

While prior reviews have highlighted the role of single-species membranes in drug delivery [9] or non-GBM-targeted membranes in drug delivery [10], a holistic analysis of diverse membrane sources (*e.g.*, stem cells, hybrid systems) and their engineering strategies (*e.g.*, CRISPR-based editing, aptamer

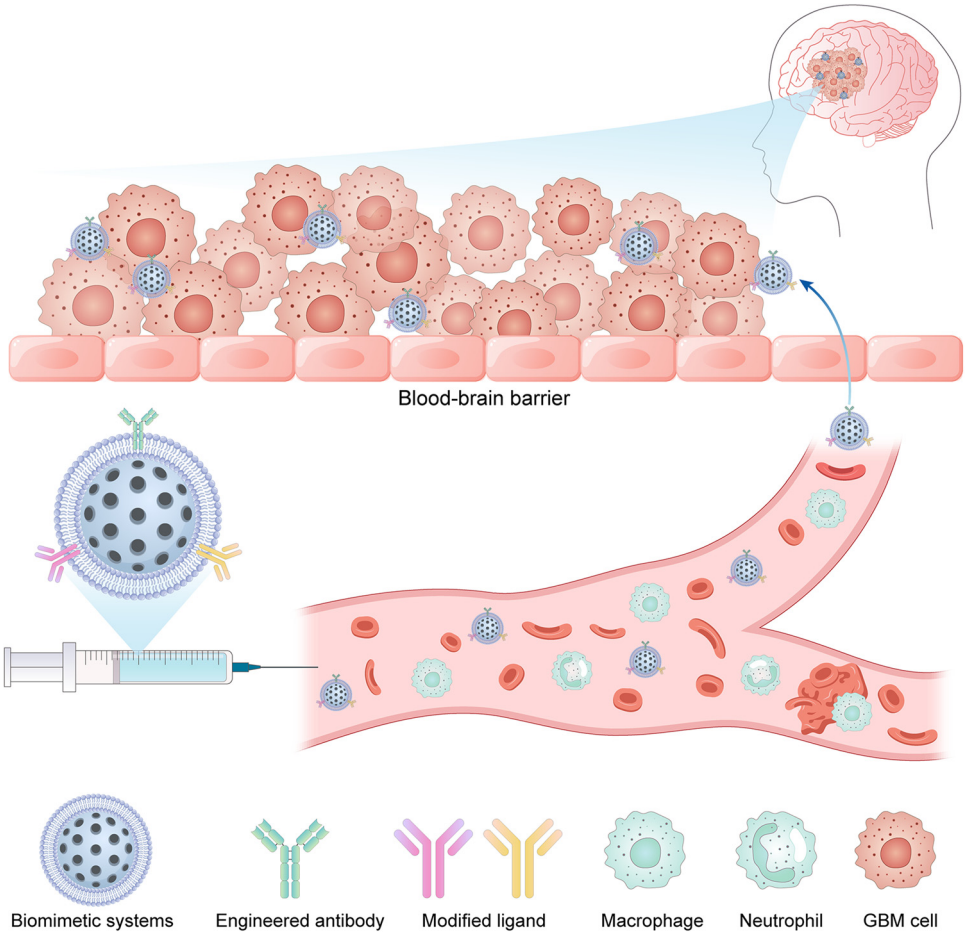

Figure 1: Schematic representations of the delivery process of the biomimetic system to the GBM. The engineered or ligand-modified biomimetic membrane system avoids phagocytosis by immune cells such as macrophages and neutrophils in the blood circulation, penetrates the BBB, and targets native GBM in the brain. Created with BioGDP.com [101].

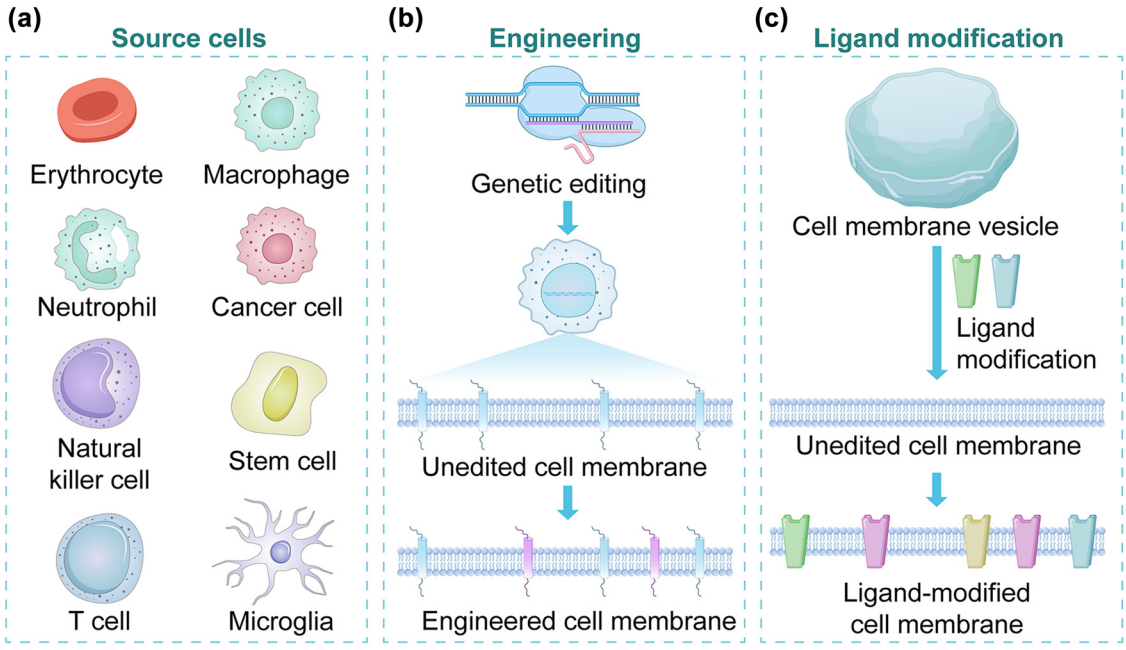

Figure 2: Schematic representations of the various types and sources of CM for GBM therapy. (a) Source cells, including erythrocytes, immune cells (NK cells, T cells, macrophages, neutrophils), cancer cells, stem cells, and exosomes. (b) Performing gene editing on cells to achieve high or low expression of membrane surface receptors. (c) Modifying the CM with ligands to equip the surface with ligands to enhance GBM-specific binding and penetration.

conjugation) for GBM-specific applications is still absent. By integrating advances in membrane engineering and nanotechnology, this review aims to emphasize their potential to overcome the BBB and address GBM heterogeneity (Figure 3).

2 Preparation and characterization of membrane-coated nanoparticles

2.1 Isolation techniques for membranes

Ultrasonic energy can be applied to a liquid containing target cells using either an ultrasonic bath or a probe-type ultrasonicator. The sound waves cause microbubbles (cavitation nuclei) in the liquid to vibrate, grow, and accumulate energy. Once the energy reaches a critical threshold, these bubbles collapse abruptly [11]. While ultrasonic disruption enables rapid lysis and is ideal for lab-scale production, heat generation poses a risk of protein denaturation. To mitigate this, precise temperature control or cold media are required. Unlike detergent-based chemical lysis, ultrasonication avoids surfactant residues that disrupt membrane protein functionality and nanoparticle biocompatibility [12].

The freeze–thaw method involves multiple cycles of freezing and thawing the sample suspension. Ice crystals formed during freezing cause the cells to expand, and thawing results in contraction, ultimately rupturing the cell walls. Typically, two to three freeze–thaw cycles are needed for effective cell disruption and are less efficient for nucleated cells. This method is widely used in extracting platelet membranes due to its gentle mechanical disruption, which preserves membrane-associated receptors [13], though it may affect the activity of sensitive enzymes [9].

A hypotonic solution has a lower concentration of impermeable solutes than the solution inside the cell. When cells are exposed to a hypotonic environment, water enters the cell, causing it to swell and potentially lyse. RCBs, which lack nuclei, are particularly sensitive to hypotonic solutions and prone to swelling [8]. This technique is superior to enzymatic digestion for erythrocyte membrane (EM) isolation, as enzymes degrade surface markers critical for tumor targeting. However, hypotonic treatment has low efficiency in breaking open nucleated cells. Therefore, homogenization is often used after hypotonic treatment to further fragment and disperse cells [14]. Homogenization is effective for a wide range of cells, including neutrophils, cancer cells, and even mitochondria.

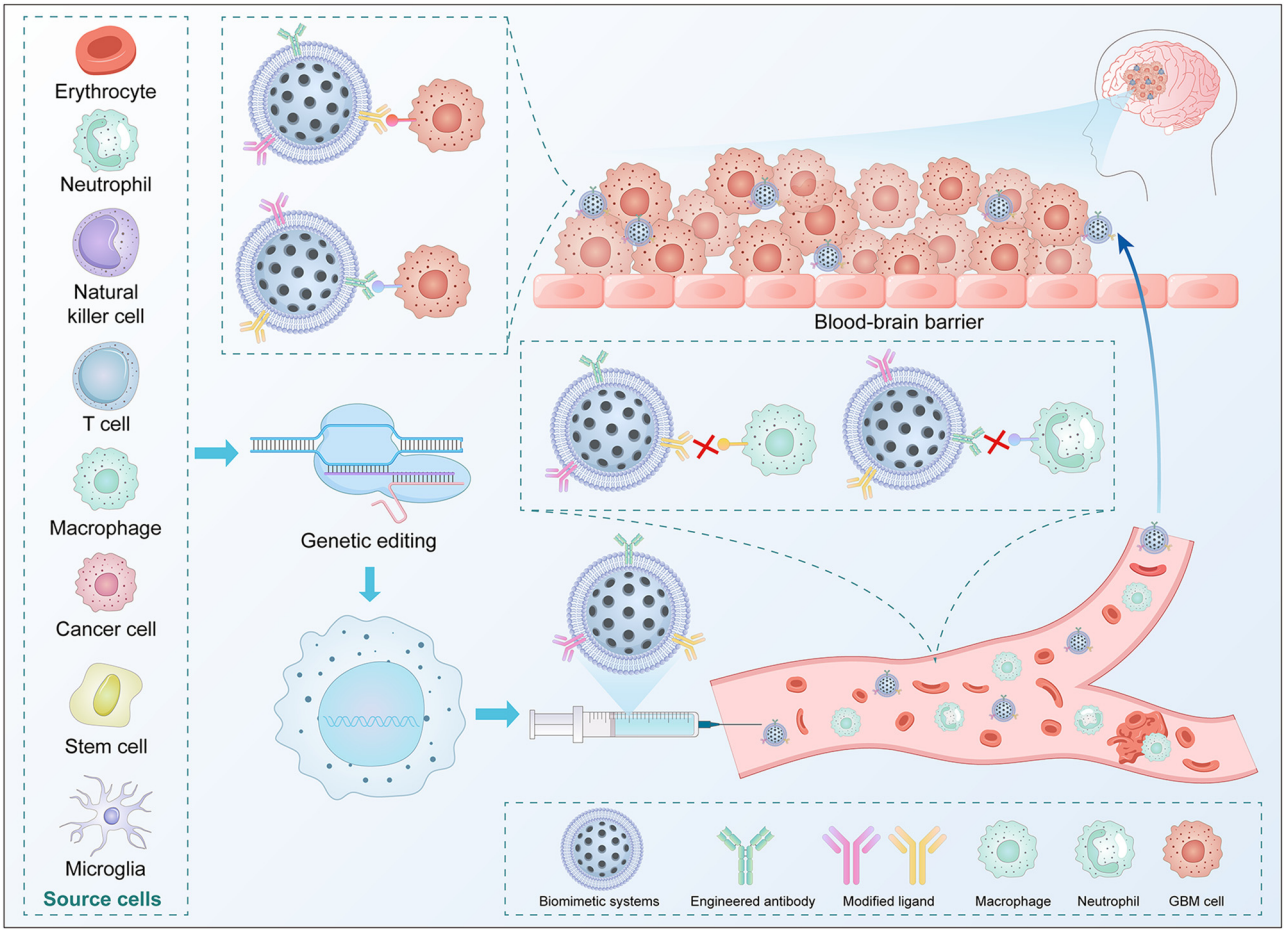

Figure 3: Schematic overview of membrane-based biomimetic systems for GBM therapy. Diverse CM sources can be engineered through gene editing or ligand modification and then coated onto drug-loaded nanoparticles to create advanced delivery systems. These biomimetic nanoparticles leverage natural membrane properties to evade immune clearance, penetrate the BBB *via* RMT, and specifically accumulate in GBM tissue through homotypic recognition or ligand–receptor interactions.

2.2 Coating methods for applying membranes onto nanoparticles

The main methods for coating nanoparticles with membranes are physical extrusion, sonication, and microfluidic electroporation. Extrusion is a simple physical method that does not damage the CM. It involves passing membrane vesicles and nanoparticles through nanoporous channels, causing them to fuse and form core–shell membrane-coated nanoparticles. The size of the resulting biomimetic nanosystems depends on the pore size [15]. While this method is effective, it is not suitable for large-scale production, limiting its potential for clinical applications.

Sonication uses ultrasonic energy to disperse CM layers. This technique aids in various membrane fusion processes. In addition to encapsulating nanoparticles in membrane vesicles, sonication can also combine membranes with nanoparticles to form stable vesicular structures [16]. However, the heat generated during sonication can lead to protein denaturation. Therefore, the frequency, duration, and intensity of sonication must be carefully controlled to avoid affecting the properties of the resulting nanomedicines.

Microfluidic electroporation, facilitated by microfluidic chips, has gained attention due to its ability to provide reproducible and high-throughput preparation of membrane-coated nanoparticles. In this method, electric pulses help nanoparticles penetrate CM vesicles as they flow through the electroporation zone [17]. The high throughput and precision of this technique make it ideal for large-scale production, avoiding the time-consuming nature of other methods.

2.3 *In vitro* validation of membrane-coated nanoparticles

Once membrane-coated nanoparticles are prepared, it is essential to assess their characteristics to ensure optimal

performance. Below, we delve into the key factors for validating the coating process *in vitro* (Figure 4).

Surface morphology provides an intuitive way to analyze membrane-coated nanoparticles. Transmission electron microscopy (TEM) is a critical tool for visualizing the bilayer structure of membranes. TEM employs a high-energy electron beam to penetrate ultra-thin samples (≤100 nm), generating high-resolution images due to the short wavelength of electron. For membrane-coated nanoparticles, samples are often prepared *via* negative staining to enhance contrast. The lipid bilayer appears as a distinct two-layered structure in TEM images, with thickness measurements directly obtained using calibrated image analysis software [18]. This technique also enables the calculation of nanoparticle size distribution and verification of core-shell integrity.

Dynamic light scattering (DLS) measures the hydrodynamic diameter of nanoparticles in suspension by analyzing fluctuations in scattered light intensity caused by Brownian motion. A monochromatic laser irradiates the sample, and a detector captures time-dependent intensity variations at a fixed angle. These fluctuations are processed *via* an autocorrelation function, from which the diffusion coefficient is derived. DLS provides a polydispersity index, indicating sample homogeneity. Additionally, zeta potential, reflecting surface charge, is measured by applying an electric field and tracking particle mobility *via* phase analysis light scattering [19]. Membrane-coated nanoparticles generally show an increase in particle size by several tens of nanometers compared to their uncoated counterparts. The phospholipid bilayers of cellular membranes carry a negative charge, which results in a corresponding change in the zeta potential after coating with nanoparticles.

Surface proteins on the membranes contribute to immune evasion, extending the circulation time of nanoparticles *in vivo*. Some proteins also possess tumor-targeting properties, such as those specific to GBM cells. Therefore, verifying whether the coated nanoparticles carry these proteins is critical. While SDS-PAGE and Western blotting provide semi-quantitative confirmation of membrane protein and target proteins (*e.g.*, CD47) retention, their ability to assess coating uniformity and precise coverage is limited. For example, SDS-PAGE compares total protein profiles between membrane vesicles and CMNPs to estimate coating efficiency, but flow cytometry would better resolve protein distribution across individual particles [20,21]. Detection of these specific membrane proteins can also reflect the purity of the extracted CMs. Additionally, membrane fluidity may significantly influence receptor–ligand interactions, cellular uptake efficiency, and membrane fusion processes. Techniques such as fluorescence recovery after photobleaching can be utilized to quantify membrane fluidity [22,23]. However, to date, there has been a lack of research specifically focusing on the outer membrane fluidity of membrane-coated nanoparticle delivery systems. This highlights an area where future advancements and additional testing may be required to refine this technology. Ultraviolet–Visible (UV–Vis) spectroscopy can also be used to compare raw nanoparticles with

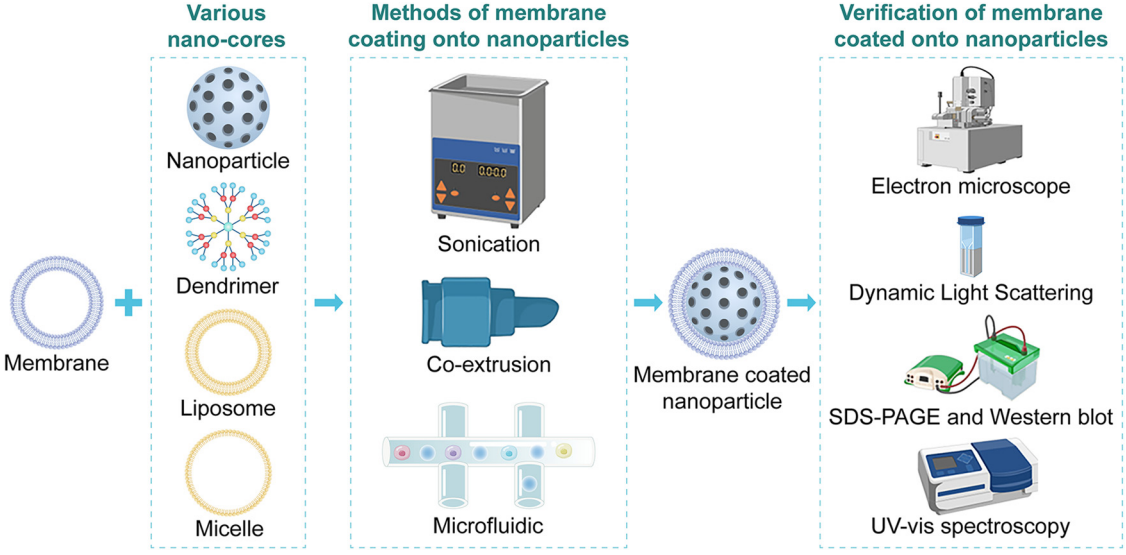

Figure 4: Schematic representations of the preparation and *in vitro* verification of membrane-coated nanoparticles. Key steps include: (1) isolation of CMs *via* techniques like hypotonic lysis or freeze-thaw cycles, (2) coating nanoparticles using extrusion, sonication, or microfluidic electroporation, and (3) validation *via* TEM (core–shell structure), DLS (size/zeta potential), SDS-PAGE/Western blot (protein retention), and UV–Vis. Created with BioGDP.com.

membrane vesicles, with new absorption peaks indicating successful encapsulation of the membrane vesicles within the nanoparticles [24].

3 Membrane-based biomimetic drug delivery systems

3.1 EM

RBCs are the most abundant and longest-living cells in the blood, with a circulation lifespan of 100–120 days [25]. The surface of EM is decorated with specific polysaccharides and proteins, such as CD47, which help RBCs navigate through the cardiovascular and cerebrovascular systems and normal tissues without being recognized or engulfed by the reticuloendothelial system [26]. Additionally, EM are thin, flexible, and easily deformable, enabling them to pass through small blood vessels and capillaries. This property also facilitates their ability to cross the BBB [27]. Moreover, EMs are rich in proteins and macromolecules that support membrane stability and function. In nanodrug delivery systems, the biomimetic modification of nanoparticles with EMs has emerged as a promising strategy for achieving prolonged circulation and BBB penetration, offering vast potential for therapeutic applications.

Although EMs are effective in crossing the BBB, their inherent ability to recognize and target tumors is limited. As such, EMs are often modified with targeting peptides to enhance their tumor-targeting capability, particularly for treating GBM and other cancers [28].

3.1.1 iRGD modified

iRGD is a novel tumor-homing peptide derived from the traditional RGD sequence, consisting of nine amino acids. It binds initially to αv integrins on tumor cells and blood vessels. Protease cleavage exposes the CRGDK/R fragment, which then binds to neuropilin-1 (NRP-1), effectively facilitating tumor infiltration [29]. Additionally, iRGD increases the permeability of tumor blood vessels, reduces the interstitial pressure within the tumor, and enhances the diffusion of small-molecule drugs. Nanoparticles and drugs conjugated with iRGD can efficiently reach tumor sites, thereby minimizing side effects [30].

Luo *et al.* developed iRGD-modified EM-coated nanodots (iRGD-EM:TNDs) for the treatment of GBM [31]. This biomimetic system, which combines the stealth properties of EM with the tumor-penetrating ability of iRGD, successfully inhibited GBM growth and increased the 30-day survival rate from 0 to 100%. *In vitro* and *in vivo* studies (including BBB models) demonstrated that iRGD-EM:TNDs were able to cross the BBB and accumulate in glioma tumors, outperforming both unmodified nanodots and EM:TNDs.

3.1.2 ApoE modified

Research has revealed the presence of multiple receptors on the BBB that facilitate receptor-mediated transcytosis (RMT), including the low-density lipoprotein (LDL) receptor (LDLR) family, transferrin receptors (TfR), and insulin receptors. Notably, the upregulation of LDLRs, such as LDLR, LRP1, and LRP2, is associated with GBM progression [32]. These receptors are also overexpressed on GBM cells, making them an ideal target for drug delivery. Among the peptides that target LDLRs, the ApoE peptide – a tandem dimer of the receptor-binding domain – has been shown to enhance brain drug delivery efficiency without interfering with endogenous apolipoprotein E [33].

Liu *et al.* utilized ApoE-modified EMs to encapsulate TMZ and OTX015, a bromodomain inhibitor, in nanoparticles (ABNM@TMZ/OTX) for GBM co-delivery [34]. Through the encapsulation with ApoE-modified EM, the ability of NP-mediated GBM targeting and BBB penetration for therapeutic delivery was significantly improved, which was achieved by greatly enhanced blood circulation time. In addition, the treatment exhibited excellent safety profiles in safety assessments, ensuring the safety and efficacy of the therapeutic process.

Similarly, Zhang's research prepared ApoE-modified EM-coated nanogels loaded with TMZ and ICG (ARNGs@TMZ/ICG) [35]. Compared to the original nanogels, camouflaging the nanogels with apolipoprotein E peptide-decorated EM not only facilitates prolonged blood circulation and enhances active tumor targeting but also makes them more effective in inhibiting GBM through NIR activation.

3.1.3 Ang modified

Among the numerous targeting sites for GBM, Ang-2 (Angiopep-2) has garnered significant attention due to its unique brain-targeting properties and efficient drug delivery capabilities [36,37]. Ang-2, a short peptide composed of 19 amino acid residues (TFFYGGSRGKRNNFKTEEY), specifically recognizes and binds to the highly expressed membrane receptor, low-density lipoprotein receptor-related protein (LRP), found on brain capillary endothelial cells and GBM

cells. This binding not only mediates the transport of therapeutic drugs across the BBB into the brain but also achieves efficient accumulation of the drugs at the glioma lesion sites within the brain [38].

The Cu chelator di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone (Dp44mT), despite its potent anti-tumor activity, faces limitations in application due to its nonspecific systemic toxicity. Ismail *et al.* designed an Ang-2-modified EM camouflaging NP carrier, co-loading Dp44mT and regadenoson (Reg) (Ang-MNPs@(Dp44mT/Reg)) [39]. This system is capable of crossing the BBB and specifically targeting Dp44mT to the orthotopic GBM sites in the brain. It significantly prolonged the median survival time of Cu-enriched orthotopic U87MG-Luc mice. Furthermore, due to the encapsulation with EM and the precise targeting of Ang, the delivery system exhibited negligible systemic drug toxicity in mice, demonstrating its potential for use in other neurological diseases. In another study, Liu *et al.* also employed Ang-2-modified EM to camouflage siRNA-loaded nanoparticles (Ang-RBCmCA/siRNA), exhibiting excellent biocompatibility and efficient targeted uptake by GBM [27].

3.1.4 CDX modified

CDX, a short peptide composed of 16 amino acid residues (FKESWREARGTRIERG), derived from candoxin, exhibits a robust binding affinity for nicotinic acetylcholine receptors (nAChRs) and has been validated for its capacity to cross the BBB [40]. ^{D}CDX peptides, which represent the retro-inverso isomers of their ^{L}CDX counterparts, exhibit complete resistance to proteolysis. Notably, ^{D}CDX peptides demonstrate an even greater binding affinity for nAChRs compared to ^{L}CDX. Liposomes modified with ^{D}CDX have shown promising BBB-penetrating abilities, leading to significant therapeutic outcomes in the treatment of GBM when encapsulated with doxorubicin (DOX) [41].

Chai *et al.* endowed EM with potent GBM targeting capability by modifying them with CDX. *In vivo* experiments have confirmed that ^{D}CDX-modified EM nanoparticles (^{D}CDX-RBCNPs) exhibit enhanced GBM targeting ability and therapeutic efficacy, while simultaneously markedly reducing toxicity compared to non-targeted drug formulations [42].

3.1.5 Aptamer modified

Aptamers, a class of molecules first described in the 1990s, represent a unique category of short RNA or single-stranded DNA oligonucleotides [43]. These oligonucleotides are remarkable for their ability to exhibit specific recognition and high affinity toward target molecules. They possess particular advantages, including convenient synthesis, smaller size, easy modification, good stability, and non-immunogenicity [44]. In comparison to peptides or antibodies, aptamers offer these benefits. CLN0003_SL1 (SL1), a meticulously designed 50-nucleotide DNA aptamer specifically tailored to bind to the c-Met protein, has exhibited the ability to inhibit HGF-stimulated activation of c-Met. Additionally, this aptamer holds significant potential for enhancing the effective delivery of nanoparticles into intracranial GBM, particularly as c-Met is predominantly overexpressed in the mesenchymal phenotype of GBM [45].

Liu *et al.* have developed a method of modifying EM with aptamer SL1 to encapsulate DOX-loaded RNP (SL1-RNP-DOX), enabling targeted therapy against c-Met-expressing GBM [46]. Compared to conventional formulations, SL1-RNP-DOX not only exhibits superior tumor localization but also significantly extends the median survival time of GBM mice to 23 days.

3.1.6 TfR aptamer modified

TfR represents a promising target for GBM, as its expression in tumor cells is significantly higher than that in normal brain cells [47]. T7, a TfR-binding peptide, has potential as a useful ligand for targeted delivery to GBM, and modifying nanocarriers with T7 peptide holds great promise for the treatment of GBM. After intravenous administration, the T7 peptide exhibits high permeability across the BBB, resulting in high accumulation in GBM tissues, thereby offering dual functions of high targeting and high permeation [48]. Although there is currently no research on the use of TfR aptamer-modified EM for GBM treatment, this does not detract from the significance of TfR aptamer modification as an important research direction for targeted GBM therapy.

3.2 Immune CM

During tumor progression, various cytokines and chemokines are released, which serve as chemotactic signals to recruit immune cells, including neutrophils (NEs), macrophages, natural killer (NK) cells, and T cells, into the tumor microenvironment. Despite the presence of tumor immune escape mechanisms such as immune cell exhaustion that hinder the natural clearance function of these cells, their tropism toward tumors still offers targeting potential and therapeutic promise for drug delivery. Therefore, it is conceivable to harness the mutual recognition between

surface antigens and antibodies on both entities to construct immune CM-biomimetic drug delivery systems for targeted antitumor drug delivery.

3.2.1 NE membrane

NEs, as a crucial member of the immune system, constitute a significant proportion of the total white blood cell count in the human body, ranging from 40 to 75% [49]. NEs exhibit remarkable chemotaxis, enabling them to migrate deformably toward inflammatory sites, particularly those surrounding tumors. During acute inflammatory responses, NEs are rapidly activated and migrate from the circulatory system to the site of inflammation [50]. Notably, NEs possess the inherent ability to cross the BBB and accumulate at the GBM, where they interact with circulating tumor cells (CTCs) through adhesion molecules such as LFA-1, L-selectin, and β1-integrin, binding to ligands like ICAM-1, CD44, and VCAM-1 on the CTCs [51,52]. However, with a half-life span of only 7 h of NEs and their difficulty in being cultured *in vitro* limit their direct application as drug delivery carriers [53]. Nevertheless, the extraction of NE membranes and their utilization for tumor targeting provide a promising target for GBM-directed therapies.

Chen *et al.* developed PLGA-PEG-DOX nanoparticles coated with NE-like membranes derived from immortal HL60 cells (NM-PD) for the treatment of post-surgical residual GBM [54]. Given that surgical resection of GBM induces localized tissue damage and elicits an acute inflammatory response, leading to the accumulation of peripheral NEs within the inflamed brain tissue, the NM-PD nanoparticles, equipped with NE-like membranes, can be activated by chemokines and navigate along the chemotactic gradient. Subsequently, they traverse the BBB and concentrate on the residual GBM tissue adjacent to the surgical margin. This targeted accumulation facilitates the localized release of DOX, effectively inhibiting the residual GBM cells. The results of *in vivo* tissue distribution experiments showed that NE CMs activated by LPS exhibited stronger GBM aggregation capability compared to unactivated NE cells. Furthermore, the study found that the aggregation ability of NEs toward GBM was greater in resected mice than in non-resected mice, indicating that NEs navigate toward GBM by following the chemotactic gradient.

3.2.2 NK membrane

NK cells are a crucial component of the innate immune system, capable of producing pro-inflammatory cytokines to kill cancer cells [55]. NK cells possess cytotoxic functions similar to T cells, but unlike T cells, they do not require prior antigen-specific activation or sensitization to recognize and eliminate tumor cells, including GBM cells. After recognizing GBM cells, NK cells lyse the tumor cells through granzymes and perforin, and can also induce tumor cell death by binding to death receptors on the tumor cells [56]. Due to their strong ability to recognize GBM, the membrane of NK cells can also be used as a biomimetic system for targeting GBM.

To enhance the effectiveness of GBM immunotherapy, Zhang *et al.* constructed a cRGD-decorated NK CM-coated nanoparticle (R-NKm@NP) co-loaded with TMZ and interleukin-15 (IL-15), aiming to improve the immunosuppressive microenvironment of GBM [57]. The experiment verified the successful encapsulation of the NK CM onto the nanoparticle by detecting the presence of NKp30, NKG2D, and CD56 proteins. R-NKm@NP notably extended the half-life of TMZ and bolstered its capacity to accumulate in orthotopically implanted GBM in mice. *In vivo* studies demonstrated that following R-NKm@NP treatment, there was an increase in the infiltration of NK cells and $CD8^+$ T cells within the tumor microenvironment, thereby enhancing the efficacy of immunotherapy.

3.2.3 Macrophage membrane

Among the leukocytes associated with cancer, a significant portion are macrophages, which can differentiate into two types of TAMs: M1 and M2 [58]. The M1 type, also known as "big eaters," utilizes phagocytosis to engulf and degrade invading substances and cancer cells, specifically targeting the inflammatory tumor microenvironment. Additionally, the presence of macrophage-1 antigen (Mac-1) and integrins α4 and β1 on the surface of macrophages enables them to interact with vascular cell adhesion molecule-1 (VCAM-1) expressed on tumor vasculature, thereby imparting them with robust tumor targeting capabilities [59]. In the tumor microenvironment, macrophages develop a unique phenotype that shares characteristics with M2 macrophages, functioning as supportive cells for tumor progression by producing cytokines or stimulating endothelial cell proliferation and angiogenesis [60]. Given that macrophages possess the ability to cross physiological barriers and escape immune recognition, combined with their tumor-targeting properties, macrophage membrane-coated nanoparticles have been incorporated into drug delivery systems. Interestingly, macrophage membranes derived from M2 macrophages exhibit a stronger targeting ability toward GBM compared to those derived from M1 macrophages, potentially due to the high expression of integrin CD49d [61].

Lai *et al.* created MDINPs, which are nanoparticles disguised as macrophage membranes and loaded with an NIR-Ib fluorescence dye [62]. These MDINPs can cross the BBB, accumulate at tumor sites for targeted imaging, and destroy tumor cells through photothermal effects. The experimental results indicated that coating with macrophage membranes could not only significantly enhance the stability of IR-792, reducing systemic toxicity, but also improve the cellular uptake of the nanoparticles by GBM cells, which facilitates a more effective combination with laser treatment.

The incorporation of targeting peptides on the macrophage membranes will further elevate the targeted delivery efficiency of the nanodelivery system toward GBM. The Ang-2-modified macrophage membrane-coated nanoparticles loaded with saRNA (ALOX15) (Ang-MM@saNPs) constructed by Cao *et al.* can effectively induce ferroptosis in GBM by promoting mitochondrial damage [63]. The application of biomimetic systems not only reduces the clearance of nanoparticles by the MPS but also enhances their ability to cross the BBB. Furthermore, these biomimetic nanoparticles exhibited a favorable safety profile and did not cause any notable side effects, even when administered to mice over an extended period.

The ease of acquisition and *in vitro* cultivation of macrophages provide the possibility for functional modification of macrophages. Yin *et al.* successfully obtained macrophages with high expression of PD-1 by introducing the PD-1 gene into them [64]. After the macrophage membranes, which carry nanoparticles, cross the BBB, and reach the tumor microenvironment, the highly expressed PD-1 on the membranes binds to PD-L1 on the surface of GBM cells. This approach can optimize the local activity of PD-1, enabling it to competitively bind to PD-L1 and thereby efficiently inhibiting the PD-1/PD-L1 signaling pathway. By blocking this immune checkpoint, it activates $CD8^+$ CTL cells to kill GBM cells.

3.2.4 T CM

Unlike most white blood cells, T cells primarily reside in the thymus after migrating from the bone marrow, where they undergo differentiation and development [65]. The diverse receptors distributed on the surface of T cells act as “precision keys” in the immune system, ensuring that the immune system can generate appropriate responses to all potential antigens. Notably, the receptors expressed on T lymphocytes can precisely recognize and bind to tumor-derived antigens, locking onto cancer cells with extremely high affinity [66]. This highly specific and efficient tumor recognition capability of T cells suggests that their membranes have the potential to become ideal nanocarriers for targeted drug delivery in cancer immunotherapy.

Wang and his colleagues genetically engineered an anti-CD133/EGFR chimeric antigen receptor (CAR) construct, which was anchored on the surface of T cells [67]. This CAR construct incorporated a constitutive EF1α promoter, the 4-1BB costimulatory domain, and the CD3ζ intracellular signaling domains, all specifically designed to target CD133 and EGFR. Furthermore, this T-CM was coated onto nanoparticles possessing aggregation-induced emission (AIE) properties, resulting in CM@AIE NPs for the treatment of GBM. By modifying the T-CM and its targeting receptors, the nanoparticles were able to efficiently penetrate the BBB and specifically target both GBM cells and GSCs. Experimental results demonstrated a high accumulation of CM@AIE NPs at the brain tumor site. With the assistance of photothermal therapy (PTT), these nanoparticles significantly killed both tumor cells and stem cells, which serve as the source of tumor recurrence. This innovative approach combines the advantages of targeted delivery and photothermal ablation, offering a promising strategy for the treatment of GBM.

3.2.5 Microglia membrane

Microglia are unique immune cells within the CNS that play a crucial role in the brain microenvironment. As a type of neuroglial cell, microglia not only possess the functions of immune surveillance and inflammatory response but are also responsible for clearing pathological cells and harmful substances [68]. These cells are characterized by their multiple synapses and high plasticity, exhibiting a slender morphology with multiple branching protrusions in their resting state. However, upon stimulation or immune activation, they can rapidly transform into a macrophage-like state, with an enlarged cell body and extended protrusions, thereby better performing their immune functions [69]. Notably, microglia can effectively cross the BBB and specifically target the GBM area through the CX3CL1/CX3CR1 and CSF1/CSF1R signaling axes [70,71]. By cloaking delivery systems with microglia membranes, the ability of these systems to breach the BBB and accurately target the GBM microenvironment can be significantly enhanced, potentially elevating the efficacy of GBM treatments.

Qiao *et al.* have developed microglia membrane-coated nanoparticles loaded with zoledronic acid (ZOL@CNPs) that actively target the orthotopic site of GBM along the CX3CL1/CX3CR1 and CSF-1/CSF-1R signaling axes for the treatment of TMZ-resistant GBM [72]. The research findings reveal that ZOL@CNPs induce apoptosis in TMZ-resistant

GBM and ameliorate the immunosuppressive and hypoxic microenvironment conducive to GBM proliferation. This study highlights the superiority of microglia membrane-coated nanoparticles in targeting GBM.

3.3 Cancer CM

Cancer cells exhibit the remarkable ability to proliferate indefinitely, making them readily obtainable through *in vitro* cultivation. This characteristic establishes a solid foundation for the collection of large quantities of CM. Notably, the surface of CM often overexpresses CD47, a "don't eat me" signal protein, which enables it to evade the immune system [73]. Furthermore, these membranes inherit the functions of homologous targeting and antigen reservoirs from their source cells. These functionalities are primarily attributed to membrane-bound proteins such as N-cadherin, selectins, cadherins, and integrins, which facilitate the homotypic aggregation of transformed cells [74,75]. Consequently, CM possesses an innate homotypic tumor-targeting capability.

To enhance the effectiveness of the combination therapy of TMZ and cisplatin (CDDP) for GBM, Zou *et al.* developed CM camouflaged nanoparticles that co-deliver TMZ and CDDP, enabling *in situ* drug release at the GBM site [76]. These nanoparticles exhibited stronger GBM inhibitory effects and prolonged survival compared to equivalent doses of free drugs.

CM can also be modified with various targeting peptides. The TfR aptamer-modified brain metastatic tumor CM, designed by Su and colleagues, encapsulates nanocomplexes containing Pep-TPE and siRNA (TMPsM) [77]. This design provides dual targeting capability and prolonged blood retention, helping the nanocomplexes achieve precise tumor localization and dynamic transglutaminase 2 activity detection, thereby enabling accurate diagnosis.

To maximize the efficacy of CM homologous targeting, Zhang and his team utilized CM derived from GBM patients (GBM-PDTCM), which may exhibit a higher degree of homology to GBM tumors compared to the *in vitro* cultured GBM CM [78]. GBM-PDTCM, when coated with gold nanorods (GBM-PDTCM@AuNRs), is utilized for precise surgical resection and PTT of GBM. Research indicates that GBM-PDTCM@AuNRs possess the capability to efficiently cross the BBB and selectively target GBM, generating intense fluorescence signals at the tumor's core and sensitive Raman signals at its margins. Consequently, by integrating fluorescence imaging and Raman spectroscopy, GBM tissue in U87MG orthotopic xenograft mice can be removed thoroughly and accurately, maximizing the tumor removal rate during GBM surgery within a very short period. Additionally, GBM-PDTCM facilitates the entry of GBM-PDTCM@AuNRs into GBM cells, enhancing the photothermal effect of the gold nanorods.

3.4 Stem CM

Neural stem cells (NSCs) exhibit a remarkable ability to target and penetrate intracranial tumor tissues. In studies involving experimental intracranial gliomas in adult rodent models, after implantation, NSCs demonstrated highly migratory properties [79]. They not only rapidly and extensively distributed within the tumor but also migrated to the contralateral cerebral hemisphere or into the cerebral ventricles. Notably, these donor cells specifically migrated into normal tissue to target tumor cells, including human GBM. This migration was not random but rather specific to the tumor, as if the NSCs were able to "track" the infiltrating tumor cells that had migrated away from the primary tumor mass. Furthermore, when NSCs were implanted intravascularly outside the CNS, they were still able to accurately target intracranial tumors. This unique targeting and migratory ability makes NSCs an excellent source for biomimetic membranes. Jia *et al.* introduced a strategy where the oncolytic virus (A4/k37) was coated with NSC membranes for targeted therapy against GBM. This approach not only enhanced the targeted infectivity toward GBM but also evaded immune system clearance *in vivo* [80].

Mesenchymal stem cells (MSCs) are a type of adult stem cells possessing self-renewal capability and multipotent differentiation potential. They can be isolated from various tissues, such as bone marrow, adipose tissue, and umbilical cord blood, and are easily expanded and cultured *in vitro* [81]. In the context of tumor therapy, MSCs exhibit robust tumor-targeting ability and tumor penetration. They have the capacity to spontaneously migrate toward the tumor site, a process primarily mediated by inflammatory cytokines within the tumor microenvironment [82]. These cytokines bind to receptors on the surface of MSCs, creating a potent chemotactic gradient that directs the migration of MSCs toward the tumor site. Furthermore, MSCs possess exceptional tumor penetration ability, enabling them to reach deep within the tumor. Wang *et al.* developed a novel approach for targeting GBM post-radiotherapy. They engineered MSCs to overexpress CCR2 and coated these cells with their membranes around nanoparticles containing PD-L1 antibodies [83]. Driven by

the tropism toward the abundant chemokine ligand CCL2 present in irradiated gliomas, this nanoplatform achieves targeted delivery to the tumor site. In response to X-ray radiation, it delivers checkpoint blockade antibodies and enhances tumor radiosensitization. This innovative strategy not only augments the efficacy of radioimmunotherapy for GBM but also reduces the incidence of immune-related adverse events.

3.5 Exosome

Exosomes are extracellular vesicles ranging in size from 30 to 200 nm, originating from the gradual evolution of small vesicles produced by cellular endocytosis into multivesicular bodies, which are then released upon fusion with the CM [84]. They not only participate in intercellular material exchange and information transfer but also demonstrate significant potential in disease diagnosis and treatment [85]. Exosomes derived from adipose tissue-derived MSCs (ASC-EVs) of a patient were extracted for the treatment of GBM [86]. The research results indicated that ASC-EVs could be substantially internalized by various human GBM cells, inhibiting their proliferation and invasion, as well as affecting neovascularization. Exosomes can carry a variety of biomolecules, including proteins, lipids, and nucleic acids, and enter target cells through direct fusion, receptor–ligand interaction, or endocytosis, enabling precise delivery. Notably, due to their ability to cross the BBB and bypass the P-glycoprotein drug efflux system, exosomes exhibit unique advantages in the treatment of GBM-related diseases [87].

Liang *et al.* prepared exosomes modified with angiopep-2 and CD133 RNA aptamers to load TMZ and O6-benzylguanine for targeting the brain [88]. By inhibiting the activity of O6-alkylguanine-DNA alkyltransferase, the therapeutic effect of TMZ was enhanced. This dual-targeting exosome carrier was confirmed to have strong intracranial GBM targeting ability through *in vivo* fluorescence imaging, which could improve survival time while also exhibiting good biocompatibility. Targeting modification of exosome vesicles for GBM seems to be a favored approach among researchers. In another study, exosomes modified with an RGD peptide were used to load DOX and siRNA, which also demonstrated strong targeting effects on GBM cells and inhibitory effects on their proliferation [89]. Genetic editing of cells can yield gene-modified exosomes. Rahmani *et al.* obtained exosomes displaying anti-EGFRvIII (ab139) antibodies on their surface through genetic editing of MSCs and used these exosomes to encapsulate cytosine deaminase (CDA) and microRNA-34a (miR-34a), achieving targeted action against EGFRvIII-positive GBM cells (U87EGFRvIII) and significantly inducing their apoptosis [90].

While experiments targeting GBM using exosomes have demonstrated encouraging outcomes, the field continues to face challenges and limitations, particularly in the realm of achieving high drug-loading capacities compared to traditional nanocarriers. Moreover, in-depth exploration is still needed in the research areas of exosome surface modification, purification, and mechanisms of action [91]. Further investigations are imperative to validate existing findings and establish definitive gold standards for exosome-based research, ultimately paving the way for clinical translation.

3.6 Hybrid CM

The unique tumor microenvironment of GBM and various obstacles encountered during targeted delivery pose stringent requirements and challenges for the camouflage delivery using a single type of CM. Thanks to the plasticity and fluidity of the lipid bilayer of CMs, the fusion and hybridization of two or even multiple CMs can enable the acquisition of specific properties from different types of CMs, thereby amplifying the characteristics of both source cells [92]. This approach can collectively address the challenges faced during GBM delivery.

A key feature of CMs is their homotypic targeting capability, which is essential for biomimetic systems aimed at targeting GBM. Currently, all hybrid CM systems used in GBM treatment incorporate CM from GBM cells. When the GBM CM is fused with NK CM [93], microglial CM [94], macrophage CM [95], other types of CM (such as B16F10) with GBM targeting ability [96], and mitochondrial membrane with organelle targeting ability [97], respectively, it demonstrates superior targeting capability toward GBM compared to using the individual CMs alone. To maximize the targeting capability toward GBM, even hybrid CMs derived from three types of cells have been employed [98,99]. These studies fully leverage the specific functions of different CMs to enhance the precision of GBM targeting.

4 Conclusions and prospects

Cell membrane-based nanotherapeutics have emerged as a promising approach for the treatment of GBM, leveraging

Table 1: Examples of membrane-based nanotherapeutics for GBM

Membrane compositions	Advantages	Limitations	Membrane source	Ligand modification	Nanoparticles	Mechanism and effect	Ref
Erythrocyte membrane	Long circulation time, immune evasion via CD47	Limited intrinsic tumor targeting, requires ligand modification	Mice erythrocyte	iRGD modified	Nanodots loaded with TMZ	Induced apoptosis	[31]
			Mice erythrocyte	ApoE modified	pH-responsive nanoparticles loaded with TMZ/OTX	inhibited cellular DNA repair, induced immunogenic cell death, inhibited PD-1/PD-L1	[34]
			Mice erythrocyte	ApoE modified	nanogels loaded with TMZ/ICG	Induced apoptosis	[35]
			Mice erythrocyte	Ang-2 modified	pH-responsive nanoparticles loaded with Dp44mT/Reg	Induced Cu-related apoptosis	[39]
			Mice erythrocyte	Ang-2 modified	pH-responsive charge-conversional siRNA complex	Gene silencing	[27]
			Mice erythrocyte	Ang-2 modified	pH-sensitive nanoparticles loaded with DOX/Lex	Induced apoptosis	[102]
			Mice erythrocyte	CDX modified	Polymeric loaded with DOX	Induced apoptosis	[42]
			Mice erythrocyte	Aptamer modified	RNP loaded with DOX	Induced apoptosis	[46]
NE membrane	Crosses BBB, responds to inflammatory chemotaxis (*e.g.*, post-surgical GBM), enhanced targeting upon activation (*e.g.*, LPS)	Short half-life (7 h), difficult to culture *in vitro*, limited direct application	HL60 cells treated with DMSO	None	Nanoparticles loaded with DOX	Induced apoptosis	[54]
NK membrane	Innate GBM recognition/killing, can carry immunomodulators (*e.g.*, IL-15), improves tumor immune microenvironment	Limited NK cell sources, may need additional modifications	NK-92 cells	cRGD modified	Nanoparticles loaded with TMZ/IL-15	Elicited an immunostimulatory TME, induced apoptosis	[57]
Macrophage membrane	Strong M2-type targeting (high CD49d), crosses biological barriers, amenable to functionalization (*e.g.*, PD-1 overexpression)	M2 phenotype may promote tumor progression, requires M1/M2 distinction, potential immunosuppressive risks	M1 (stimulated with LPS, IFNγ) and M2 (stimulated with IL-4, IL-13) RAW 264.7 cells	None	Liposome loaded with DOX	Induced apoptosis	[61]
			RAW 264.7 cells	None	Nanoparticles loaded with IR-792	Ib imaging-guided PTT	[62]
			RAW 264.7 cells	Ang-2 modified	Mesoporous polydopamine loaded with saRNA	Induced ferroptosis	[63]

(*Continued*)

Table 1: *Continued*

Membrane compositions	Advantages	Limitations	Membrane source	Ligand modification	Nanoparticles	Mechanism and effect	Ref
			PD-1 overexpressed RAW264.7 cells	None	Nanoparticles loaded with RAPA	Enhanced CTL infiltration, suppressed proliferation	[64]
			RAW 264.7 cells	ApoE modified	Nanoparticles loaded with Ce6/JQ1	Sonodynamic therapy, induced immunogenic cell death and inhibited PD-L1	[103]
T-CM	High-affinity tumor antigen targeting, crosses BBB, enhanced specificity via genetic modification	Difficult to isolate/expand T cells, genetic engineering complexity, potential immunogenicity	anti-CD133/EGFR overexpressed human T cells	None	Nanoparticles loaded with AIEgen	PTT	[67]
Microglia membrane	Innate GBM microenvironment targeting, crosses BBB, immune surveillance role	Difficult extraction/culture, activation state affects function, may contribute to pro-tumor inflammation	BV2 cells	None	Nanoparticles loaded with ZOL	Induced apoptosis, improved the immunosuppressive and hypoxic microenvironment	[72]
			BV2 cells	None	Nanosponge loaded with miRNA	Induced apoptosis, activated antitumor immune responses	[104]
			BV2 cells	None	MnP-BSA nanoparticles loaded with anti-PD-1	PTT, activated antitumor immune responses	[105]
Cancer CM	Homotypic targeting, immune evasion via CD47, easy *in vitro* expansion	Residual tumor antigens pose safety risks (*e.g.*, metastasis or immunosuppression)	U87MG and U251^{R} cells	None	pH-sensitive polymer loaded with TMZ/CDDP	Induced apoptosis	[76]
			B16F10 cells	TfR aptamer modified	Nanosponge loaded with Pep-TPE/siRNA	Self-assembly imaging, gene silencing	[77]
			U87MG cells	None	Nanotubes loaded with DOX	Induced apoptosis	[106]
			U87MG cells	None	polymer loaded with PTX/siRNA	Induced apoptosis, gene silencing	[107]
			GL261 cells	ER targeting peptide modified	polymer loaded with TBNO	Induced apoptosis, activated antitumor immune responses	[108]
			U251-TR or X01 cells	None	Nanoparticles loaded with siRNA	Gene silencing	[109]
			U87 MG or GL261 cells	None	Nanoparticles loaded with TMZ/SPIO	Enhanced the efficacy of radiotherapy, induced apoptosis	[110]
			GBM tissue from patients	None	Gold nanorods	Precised imaging, PTT	[78]
			GBM tissue from patients	None	Loaded with sodium borocaptate (BSH)	Boron neutron capture therapy	[111]

(*Continued*)

Table 1: *Continued*

Membrane compositions	Advantages	Limitations	Membrane source	Ligand modification	Nanoparticles	Mechanism and effect	Ref
Stem CM	Strong tumor tropism, crosses BBB, expandable/modifiable	Risk of pro-tumor differentiation, heterogeneity affects efficacy, may require genetic enhancement	C17.2 cells (NSC)	None	Nanoparticles loaded with oncolytic virus	Enhanced tumor infectivity, induced apoptosis	[80]
			CCR2 overexpressed mesenchymal stem cells	None	Nanoparticles loaded with anti-PD-L1	Enhanced radiosensitization, activated antitumor immune responses	[83]
Exosomes	Natural delivery mechanism, crosses BBB, low immunogenicity, versatile cargo loading (*e.g.*, siRNA, chemo drugs)	Low drug-loading capacity, purification challenges, lack of standardized production, surface modifications may alter function	Glioblastoma stem cells	Ang-2/CD133 aptamer modified	Loaded with TMZ/O^6-benzylguanine	Eradicated TMZ-resistant, induced apoptosis	[88]
			RGD overexpressed HEK293FT cells	None	Loaded with DOX and siRNA	Induced apoptosis, gene silencing	[89]
			Anti-EGFRvIII overexpressed MSCs	None	Loaded with CDA and miR-34a	Induced apoptosis by gene therapy	[90]
			adipose tissue-derived MSCs	None	None	Suppressed tumor invasiveness and vascularization in ovo	[86]
			Serum from SD rats	CpG modified	Self-assembled tanshinone IIA (TanIIA)- glycyrrhizic acid (GL) nanomicelles	Immunotherapy and chemotherapy	[112]
			Ang/TAT overexpressed HEK293T cells	None	Loaded with DOX	Induced apoptosis	[113]
Hybrid membrane	Synergistic functions (*e.g.*, BBB penetration + targeting), multi-signal pathway enhancement (*e.g.*, CM + NK membrane)	Complex preparation (optimizing membrane ratios), stability issues (lipid bilayer compatibility), potential increased immunogenicity	U87MG cells, NK cells	None	PAMAM loaded with gold nanoclusters/ miRNA	Radiotherapy, gene silencing	[93]
			U87MG cells, HMC3 microglial cells	None	Nanoflakes loaded with DOX	Induced apoptosis, induce microglia polarization	[94]
			U87MG cells, J774.A.1 macrophage cell	None	Nanoparticles loaded with ICG/siRNA	Gene silencing-enhanced sonodynamic therapy	[95]
			G422 cells, B16F10 cells	None	Liposomes loaded with ICG	Image-guided surgery	[96]
			U87MG cells, mitochondria	None	Nanoparticles loaded with Gboxin	Induced apoptosis	[97]
			U251 cells, RAW 264.7 cells, mice erythrocyte	Folate modified	Tetrahedral DNA nanocages loaded with LMP	Induced pyroptosis, inhibited MMP3 activity	[98]
			U87MG cells, HMC3 cells, THP-1 cells	None	CB [7]-PEG-Ce6 polymer loaded with MTIC	Induced apoptosis	[99]

the unique properties of CMs in combination with the advantages of nanomaterials to enhance tissue targeting capabilities for therapeutic drug delivery (Table 1). One of the key strengths of CM-coated nanoparticles lies in their ability to mimic the physiological functions of natural cells, enabling them to cross biological barriers, such as the BBB, more effectively. This is particularly crucial in the context of GBM treatment, where drug delivery to the brain poses significant challenges.

This review highlights various cell-derived membranes, including those from erythrocytes, immune cells, cancer cells, and stem cells, each with distinct properties and targeting abilities. For instance, CM exhibits innate homotypic tumor targeting due to the overexpression of specific surface proteins like CD47, making them ideal for targeting and inhibiting tumor growth. Similarly, immune CMs, such as those from NK cells or T cells, can be engineered to deliver therapeutic agents with enhanced immune targeting capabilities. However, limitations such as the short lifespan of certain cell types, like erythrocytes, hinder the large-scale extraction of CMs for GBM treatment. Therefore, developing large-scale *in vitro* culture techniques will be crucial for facilitating the extraction of these membranes in sufficient quantities. Long-term stability is another hurdle: membrane proteins degrade during storage, as evidenced by a 40% reduction in CD47 expression after 7 days [10]. Lyoprotectants like trehalose may improve shelf-life by preserving membrane integrity [100]. Furthermore, degradation kinetics and systemic toxicity require rigorous evaluation. For instance, while EM-coated nanoparticles exhibit prolonged circulation, their eventual clearance *via* the reticuloendothelial system necessitates studies on hepatic/kidney toxicity.

In addition to high targeting efficiency, CM-based nanoparticles offer other advantages, including improved pharmacokinetics, enhanced cellular internalization, and reduced immunogenicity. These characteristics make them well-suited for delivering a variety of therapeutic agents – such as drugs, biologics, and genes – for GBM treatment. However, most studies reviewed here have been conducted on animal models, and the human immune system's response to these biomimetic systems remains unknown. Immunogenicity remains a concern, as xenogeneic membranes (*e.g.*, murine erythrocytes) may trigger host immune responses, accelerating nanoparticle clearance. Autologous membrane sourcing or PEGylation strategies could mitigate this issue. Off-target effects may arise from non-specific ligand–receptor interactions; optimizing ligand density and spatial orientation through computational modeling (*e.g.*, molecular dynamics simulations) could enhance specificity. Therefore, when coating nanoparticles with different CMs, it is important to consider membrane composition (including CM proteins and glycocalyx layer) and intracellular signaling changes. *In vitro* simulation experiments are necessary to assess their immunogenicity in humans. Additionally, sourcing membrane materials from autologous or matched donors could help reduce immunogenicity.

Several coating methods, such as physical extrusion, ultrasonication, and microfluidic electroporation, can be used to apply CMs to nanoparticles. However, most of these techniques are currently at the laboratory stage, and scaling up production to a stable, reproducible, and industrially viable level poses significant challenges. Critical manufacturing hurdles include ensuring nanoparticle stability and batch-to-batch reproducibility, preventing aggregation during storage and administration, and efficient removal of cellular debris, free proteins, and lipid contaminants that could compromise purity and functionality. Moreover, hybrid CM-coated nanoparticles, which combine the properties of multiple CMs, demonstrate superior targeting capabilities compared to nanoparticles coated with a single CM type. This hybrid approach allows for the amplification of the specific properties of each membrane, enhancing the therapeutic efficacy of the nanoparticles. However, maintaining stability requires careful control of the ratio of different CMs.

Finally, leveraging the plasticity of CM phospholipids to hybridize them with lipid nanomaterials creates new materials that possess both the physical properties of nanoparticles and the functional characteristics of biological CMs. This innovative direction holds significant promise for improving GBM-targeting therapies. Similarly, optimizing the ratio of nanomaterials to CMs is essential for achieving the desired therapeutic effects.

In conclusion, CM-based nanotherapeutics represent a promising new frontier in GBM treatment. By harnessing the unique properties of CMs and nanomaterials, these therapies have the potential to revolutionize the delivery of therapeutic agents to the brain, offering more effective and personalized treatment options for GBM patients.

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