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Tumor Microenvironment-Responsive Nanocarriers for Enhanced Glioblastoma Immunotherapy

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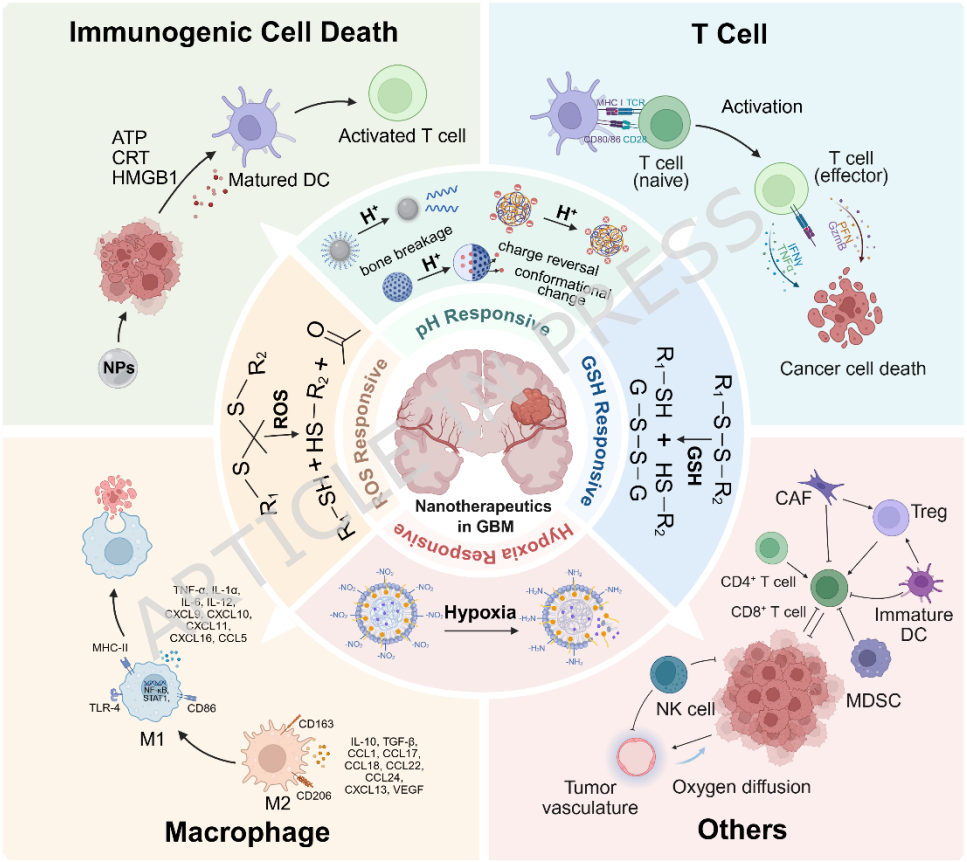
Keywords: Stimulus response; Nanocarriers; Tumor microenvironment; Immunotherapy; Glioblastoma.

Abstract:

The glioblastoma (GBM) microenvironment exhibits a profoundly immunosuppressive state, which constitutes the major barrier limiting the efficacy of immunotherapy. It is intricately intertwined with aberrant physicochemical characteristics including severe hypoxia, acidic pH, and redox imbalance. Although these physicochemical abnormalities further exacerbate immunosuppression within the GBM microenvironment, they also paradoxically serve as precise endogenous triggers for designing smart nanocarriers. By exploiting these pathological features as triggering signals, microenvironment-responsive nanocarriers can overcome the physical barriers imposed by the blood-brain barrier (BBB) and blood-brain tumor barrier (BBTB), enabling precise delivery and on-demand release of immunomodulators at lesion site. Moreover, these nanocarriers can effectively alleviate immune tolerance by reprogramming tumor-associated immune cells or inducing immunogenic cell death, thereby remodeling the immunosuppressive GBM microenvironment. This review elucidates the physicochemical and immunosuppressive features of the GBM microenvironment. Furthermore, it systematically summarizes the design principles,

cross-barrier targeting strategies, and immune remodeling mechanisms of responsive nanocarriers engineered upon tumor microenvironment (TME) characteristics. The analysis highlights the synergistic enhancement achieved through this paradigm: responding to TME signals to reverse immunosuppression. Finally, clinical translation challenges and future directions within this field are discussed to provide a comprehensive reference for designing highly efficient, GBM-targeted responsive nanoimmunotherapeutic platforms.



Graphical abstract

1. Introduction:

Gliomas, the most common primary malignant tumors formed in the central nervous system, account for approximately 80%-85% of malignant brain tumors [1-3]. Among these, glioblastoma (GBM), the most common and highly aggressive Grade IV subtype tumor in adults, presents

significant clinical challenges owing to its rapid malignant proliferation, robust therapeutic resistance, and poor prognosis [4-6]. Currently, the standard clinical regimen for GBM remains confined to maximal safe surgical resection, followed by adjuvant chemotherapy with temozolomide (TMZ) and radiotherapy [7-9]. Despite these aggressive interventions, the postoperative survival of the majority of GBM patients is <2 y, with a 5-y survival rate of <5% [10-12]. Recently, immunotherapies featuring immune checkpoint blockade (ICB), nucleic acid vaccines and small-molecule inhibitors have made remarkable breakthroughs against multiple solid tumors [13-15]. However, applying these immunotherapy strategies to GBM is confronted with formidable clinical hurdles. Regarding the current status, large-scale Phase III clinical trials evaluating ICBs and peptide vaccines have largely failed to demonstrate significant overall survival benefits in GBM patients [16]. The major challenges underlying these clinical setbacks are primarily two-fold. First, the inherent physical impedance of the blood-brain barrier (BBB) and blood-brain tumor barrier (BBTB) limits the entry of macromolecular immune drugs, causing poor accumulation at brain lesions and systemic off-target toxicities [17-19]. Second, GBM intrinsically lacks abundant neoantigens and features a highly immunosuppressive microenvironment. This environment is characterized by severe $CD8^+$ T-cell exhaustion and the massive infiltration of immunosuppressive networks, particularly M2-like tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), which aggressively exclude immune cell infiltration. This forms a formidable immune-privileged barrier, rendering traditional systemic immunotherapies largely ineffective for GBM patients [20-22]. Therefore, breaking these physiological barriers and remodeling the immunosuppressive state to enable precise, high-efficiency targeted drug delivery is crucial in GBM immunotherapy.

Tumor microenvironment-responsive nanocarriers provides a promising strategy to integrate

targeted delivery with local immune modulation. The GBM microenvironment is characterized by aberrant physicochemical properties such as severe hypoxia induced by rapid tumor proliferation, microenvironmental acidification driven by glycolytic metabolism, and a dysregulated redox state, which provide ideal endogenous signals and triggering switches for developing smart delivery systems [23-25]. Using these physicochemical characteristics of the tumor microenvironment (TME) as triggers for precise drug release, the development of stimuli-responsive nanocarriers has emerged as a pivotal strategy. Recent progress has shown that responsive nanocarriers can not only deliver immune checkpoint inhibitors, cytokines, nucleic acids, vaccines, and small-molecule immunomodulators, but also induce immunogenic cell death, reprogram tumor-associated macrophages/microglia, relieve metabolic immunosuppression, and enhance T-cell infiltration [26-28]. Integrating this strategy into GBM immunotherapy can significantly enhance the bioavailability, targeting capability, structural stability, and controlled release kinetics of immunotherapeutics, achieving optimal tumoricidal efficacy. The foundational design of these smart materials is contingent on a sophisticated stimulus-responsive spatiotemporal-controlled release mechanism. During systemic circulation, the nanocarriers maintain robust structural integrity, effectively encapsulating and shielding the immunotherapeutic agents, and minimizing systemic off-target toxicity. Upon traversing the BBB and accumulating in the tumor parenchyma, these materials specifically respond to the characteristic TME features of GBM such as low pH, hypoxia, or elevated glutathione (GSH)/reactive oxygen species (ROS) levels, triggering the precise, on-demand release of immunomodulators directly at the lesion site [29-33]. This on-demand drug release mechanism substantially elevates the bioavailability of immunotherapeutics at the tumor site and reinvigorates the antitumor immune response via localized high-concentration dosing. This process effectively reverses the immunosuppressive state of GBM, successfully

remodeling it into a robust, immune-activating microenvironment, presenting a highly promising paradigm for the precision treatment of GBM and the improvement of immunotherapeutic prognoses.

This review systematically describes the physicochemical characteristics and the immunosuppressive state of the GBM microenvironment. It summarizes the construction principles, triggering mechanisms, and immune remodeling pathways of stimuli-responsive engineered nanocarriers to exploit these specific physicochemical features. Recent research on the on-demand delivery and local functional activation of immunomodulators is also highlighted. We explored the cascade pathway connecting the TME signal response with precise drug release and the subsequent enhancement of antitumor immunity, elucidating the immense potential of this targeted delivery strategy for activating host immune responses and improving clinical prognosis (**Figure 1**). Finally, an analysis of current challenges and future directions is presented to serve as a theoretical reference for designing highly efficient, responsive nanoimmunotherapy platforms targeting GBM.

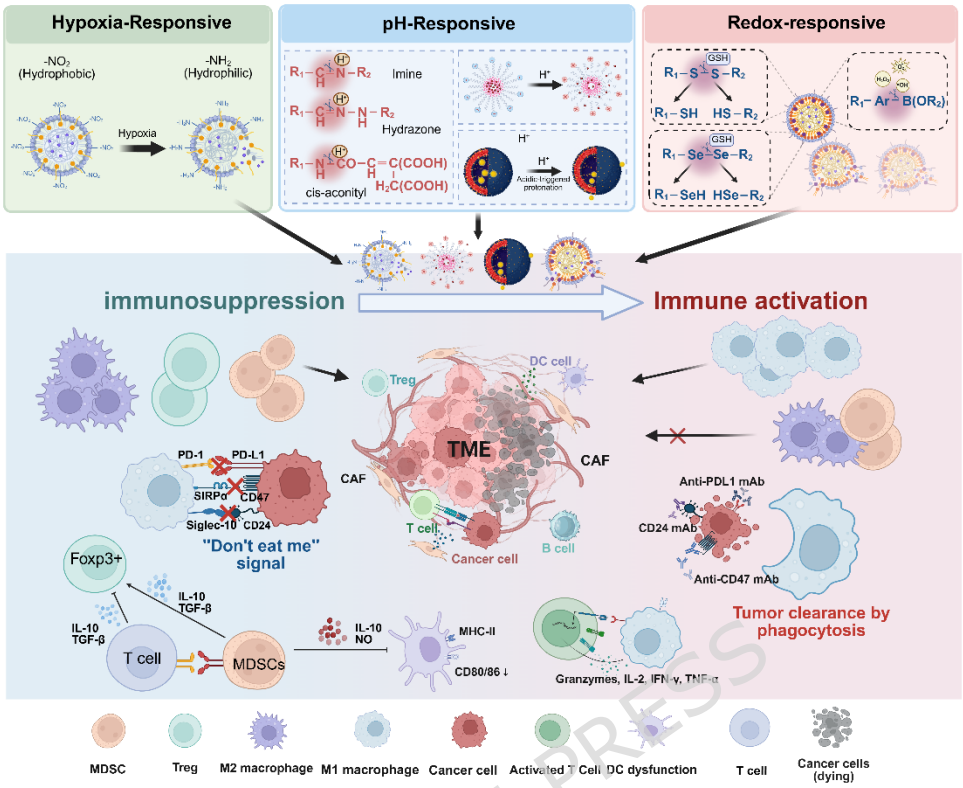


Figure 1. Diagram of stimuli-responsive nanocarriers for tumor immunotherapy. Created in BioRender. Wang, C. (2026) https://BioRender.com/2w3kj98

2. Physicochemical Characteristics of the Glioma Microenvironment

The microenvironment significantly promotes tumor progression by facilitating growth, immune evasion, and therapeutic resistance. The impact of the immunosuppressive microenvironment on GBM and the heterogeneity of its cold immune microenvironment have received increasing attention [34,35]. This microenvironment is a dynamic system comprising malignant tumor cells (including glioma stem cells), stromal cells (such as cancer-associated fibroblasts), infiltrating immune cell populations (including tumor-associated macrophages, dendritic cells, natural killer cells, and myeloid-derived suppressor cells), and a complex extracellular matrix [36,37]. Compared with normal brain tissue, this microenvironment exhibits

distinct physicochemical characteristics (**Figure 2**): (i) tissue hypoxia, a common manifestation in most solid tumors, arises from an inadequate oxygen supply caused by abnormal vasculature and excessive malignant proliferation [38,39], (ii) in GBM patients and mouse xenograft models, a median partial pressure of oxygen (pO_2) of 5–9 mm Hg and a pH of 6.8 or lower have been observed within the tumor [40-42], and (iii) high levels of ROS and GSH. These characteristics in the glioma microenvironment interact with each other and are mutually causal, but hypoxia appears to be a prerequisite for the disruption of microenvironmental homeostasis [43,44].

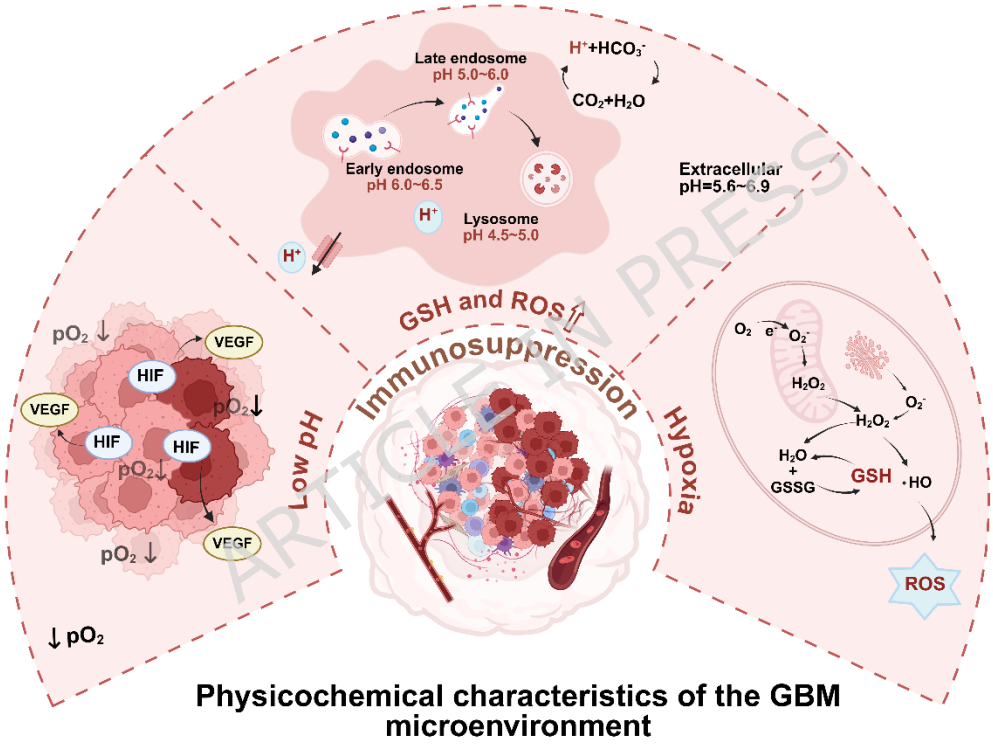


Figure 2. Physicochemical characteristics of the GBM microenvironment. Created in BioRender. Wang, C. (2026) https://BioRender.com/h5m6zrj

In GBM, the tumor core exhibits extreme hypoxia driven by abnormal vascular proliferation and malformation, and hyperactive cellular metabolism [45,46]. The microenvironment formed by the vascular proliferation in GBM patients affects the spatial distribution of glioma cells, promotes

their proliferation and invasion, and reduces the sensitivity of first-line chemotherapy drugs, including TMZ [47,48]. However, it induces the enrichment of the cell subset $CDC20^{+}KIF20A^{+}PTTG1^{+}$, which acts as a key effector of hypoxia and drives the malignant progression of the tumor, causing treatment resistance [49]. Hypoxia promotes angiogenesis by upregulating the vascular endothelial growth factor pathway, establishing a positive feedback loop linking hypoxia, angiogenesis, and immunosuppression [50]. Panoramic spatial enhanced resolution proteomics technology has confirmed that, compared with the tumor periphery and peritumoral regions, the tumor core exhibits marked hypoxia owing to vascular abnormalities and heightened metabolic activity, a key feature that shapes the immunosuppressive microenvironment of GBM [51]. Hypoxia upregulates the (i) protease legumain expression in tumor-associated macrophages (TAMs) via hypoxia-inducible factor-1α (HIF1α), (ii) glycogen synthase kinase-3β-signal transducer and activator of transcription 3 (STAT3) signaling pathway, and (iii) TAMs and cytotoxic T cells (CTLs) toward an immunosuppressive phenotype [52-54]. Additionally, hypoxia activates the protein kinase A pathway in γδ T cells at the transcriptional level, influencing γδ T cell-mediated antitumor immune responses [55]. Wu et al. reported that hypoxia might promote nuclear export signal (NES) transition through the activation of the HIF1α-FOS like 2 (FOSL2) axis. Tumor cells with a high NES activity recruit and polarize bone marrow–derived macrophages by activating the FOSL2-annexin A1-formyl peptide receptor1/3 axis. These polarized macrophages effectively suppress T-cell activity and promote NES-mediated nuclear export within the tumor. These macrophages upregulate the chemokine CCL2 to promote tumor cell migration [56]. The CCAAT enhancer-binding protein β^{+} glioblastoma subclones specifically drive the formation of M2 TAMs, promoting GBM growth [57] .

Compared with nonstem tumor cells and normal neural progenitors, HIF2α and multiple HIF-

regulated genes are preferentially expressed in glioma stem cells (GSCs). This expression pattern shapes the glioma stem cell phenotype, causing poor prognosis in GBM [58,59]. Under hypoxic conditions, the HIFα subunit dimerizes with the β subunit to control gene transcription associated with cell survival, glycolysis, pH regulation, angiogenesis, migration, and invasion by recognizing hypoxia response elements (HREs) [60,61]. HIF1α, a core member of the HIF family, is stabilized under hypoxic conditions [62]. It directly binds to HREs in the triggering receptor expressed on myeloid cells 1 promoter, thereby upregulating its expression in TAMs and promoting their polarization toward the immunosuppressive M2 phenotype ($CD163^{+}/CD206^{+}$). Transforming growth factor β2 (TGFβ2), secreted by M2-type TAMs, activates the TGFβR/SMAD2/3 signaling pathway in GSCs, significantly enhancing their stem cell-like properties, causing drug resistance in GBM and increasing its invasiveness [63].

HIF-1 plays a critical role in the metabolic shift toward aerobic glycolysis, commonly known as the Warburg effect. This shift establishes an acidic environment with a pH of <6.8, which severely disrupts immune cell metabolism and enhances the function of myeloid-derived suppressor cells (MDSCs) [64]. This metabolic reprogramming supports GBM proliferation and exacerbates malignancy by promoting lactate production and extracellular acidification. The combined effect stabilizes HIF-1α and maintains tumor hypoxia [65]. It fosters an immunosuppressive microenvironment by promoting lactate generation and adenosine accumulation, suppressing T-cell function, and enhancing regulatory T-cell activity [66]. In a mouse model of GBM, lactate production inhibitors altered the phenotype of tumor-infiltrating chimeric antigen receptor T-cells, including increased expression of the immunostimulatory IFN-γ, cytotoxic perforin, and granzyme B, and downregulated exonucleases CD39 and CD73 levels, reshaping the immune microenvironment [67]. The low pH and hypoxia in TME can affect the

mitochondria function by altering glycolysis [68,69]. Late-stage GBM features a significant accumulation of glucose transporter type 1-expressing glycolytic monocyte-derived macrophages. Within these cells, intracellular lactate-driven histone lactylation promotes the expression of IL-10 to suppress T-cell activity, resulting in profound immunosuppression and accelerated tumor growth [70]. High levels of succinate and lactate synergistically remodel the microenvironment to inhibit the infiltration and cytotoxic functions of $CD8^+$ T cells and promote immunosuppressive macrophage polarization, inducing tumor immune evasion and progression [71]. Mitochondrial dysfunction and metabolic reprogramming induced by hypoxia and acidosis compel glioma cells to significantly upregulate their oxidative defense systems, with robust ROS, GSH, and associated metabolic enzyme expression [72,73]. High levels of ROS inhibit the infiltration and function of CTLs and natural killer (NK) cells by inducing their apoptosis or exhaustion. Under oxidative stress, immunosuppressive cells such as TAMs and MDSCs readily polarize toward an immunosuppressive phenotype, further reinforcing immune tolerance by secreting factors such as TGF-β and IL-10 [74].

GBM cells promote the recruitment of TAMs by secreting various chemokines. Colony-stimulating factor 1 (CSF-1) and monocyte chemoattractant protein-1 (MCP-1), two chemokines, act as chemotactic agents for TAMs and reprogram them into an immunosuppressive and protumoral phenotype. CSF-1R blockade effectively slows the intracranial growth of patient-derived glioma xenografts [75]. TAMs release cytokines such as IL-2, IL-6, IL-1β, and CCL-8, and other factors including stress-induced protein 1, epidermal growth factor (EGF), TGF-β, and matrix metalloproteinase (MMP)-2, which enhance GBM proliferation [76,77]. They also secrete chemokines such as CCL2, CCL5, CCL20, and CCL22, which facilitate the recruitment of regulatory T cells to suppress the antitumor activities of CTLs, NK cells, and antigen-presenting

cells [78,79].

The interactions among various components of the TME collectively maintain the local homeostasis of GBM, providing the necessary conditions for tumor initiation, progression, invasion, and metastasis. The characteristics of this microenvironment simultaneously present promising opportunities for targeted therapy. Leveraging this dual nature, numerous studies have focused on stimulus-responsive mechanisms to design single-modality responsive nanoparticles (NPs) such as pH- or hypoxia-sensitive systems. Smart nanoplatforms integrating multi-responsive modules with synergistic multitarget actions were synthesized, which enhanced GBM treatment efficacy by specifically triggering drug release at the tumor site and effectively remodeling the local immune microenvironment. Exploiting the specific pathological features of the TME plays a crucial role in validating current therapeutic strategies and developing anticancer regimens for GBM.

3. Strategies for BBB and BBTB Penetration

The BBB serves as a highly selective interface that strictly regulates the entry of circulating substances into the brain. At the peripheral and invasive margins of GBM, the BBB often remains relatively intact. However, as the primary tumor proliferates, aberrant neovascularization and the deterioration of intratumoral vessels compromise BBB integrity, transforming its structure and function into what is known as the BBTB [80]. Although the BBTB is generally considered more permeable than the intact BBB, it can still express active efflux transporters and retain substantial barrier integrity. As a result, the BBTB is highly heterogeneous, with considerable spatial variability in permeability and tumor-associated vascular abnormalities [81]. During GBM treatment, both the BBB and BBTB restrict the delivery of most small-molecule drugs and protein-based therapeutics, making efficient barrier penetration a prerequisite for subsequent tumor

microenvironment-responsive activation. Nanocarriers provide a promising platform for brain tumor drug delivery because their physicochemical properties, including size, surface ligands, charge, shape, and flexibility, can be rationally engineered to enhance BBB/BBTB transport and tumor accumulation. Current strategies for enhancing BBB/BBTB penetration include receptor-mediated transcytosis, adsorptive-mediated transcytosis, transporter-mediated delivery, and biomimetic membrane camouflage. Receptor-mediated transcytosis is commonly achieved by modifying nanocarriers with ligands such as angiopep-2, ApoE-derived peptides, transferrin, lactoferrin, or RVG peptide, which target receptors or transport pathways expressed on brain endothelial cells and glioma-associated vasculature [82]. Adsorptive-mediated transcytosis and charge-modulation strategies can enhance endothelial interaction and cellular uptake, but permanently cationic surfaces may increase serum protein adsorption, endothelial toxicity, inflammation, and rapid clearance. Biomimetic carriers, including cell membrane-coated nanocarriers, extracellular vesicles, exosomes, and bacterial outer membrane vesicles, may improve immune evasion and brain tumor targeting, although their reproducibility, immunogenicity, storage stability, and large-scale manufacturing remain challenging [83]. Moreover, crossing the BBB/BBTB does not ensure deep tumor penetration. The invasive margins of glioma may retain an almost intact BBB, while dense extracellular matrix, high interstitial fluid pressure, and abnormal vasculature can restrict intratumoral nanocarriers distribution. Therefore, size-transformable nanocarriers, tumor-penetrating peptides, and extracellular matrix-modulating systems have been developed to overcome these delivery barriers and promote intratumoral transport, thereby allowing nanocarriers to reach tumor regions where they can subsequently respond to tumor microenvironmental stimuli.

4. Hypoxia-responsive

Hypoxia, an inherent characteristic of most solid tumors, plays a critical role in inducing resistance to conventional chemoradiotherapy, elevating the recurrence risk, and attenuating the efficacy of oxygen-dependent modalities such as photodynamic therapy (PDT). Hypoxia is a potent endogenous triggering signal and has been used in the design of smart, responsive nanocarriers [29,68,84]. Hypoxia-responsive NPs incorporate hypoxia-active moieties or structures, and their core mechanism primarily relies on hypoxia-sensitive elements including nitroimidazole, nitrobenzene, and azobenzene, which undergo specific chemical or structural transformations under hypoxic conditions [85]. This response mechanism effectively mitigates the risk of premature drug release in the systemic circulation and normal tissues, enabling the precise release of therapeutic agents through targeted delivery to the deep hypoxic regions of the tumor, initiating immunotherapy against GBM.

Self-assembled nanocarriers systems designed by encapsulating immunotherapeutic drugs within hypoxia-sensitive components can achieve precise drug release at hypoxic sites within tumors. Nitrobenzene represents a typical moiety, as its hypoxia-induced transformation maintains stable physical properties including color and fluorescence [86]. Xu et al. designed hypoxia-responsive lipid–polymer NPs [87], comprising a poly(nitroimidazole)core, which acts as a hypoxia-responsive trigger capable of undergoing a hydrophilic transition in postsurgical hypoxic regions exacerbated via PDT. This leads to rapid depolymerization of NPs and triggers the release of Doxorubicin (DOX), amplifying the cytotoxic effect of chemotherapy. Compared with pristine NPs, poly(nitroimidazole)-modified NPs exhibit superior antiglioma efficacy (**Figure 3A**).

Apart from using hypoxic environments to induce the physical or chemical disassembly of nanocarriers, another hypoxic-responsive strategy involves using the hypoxic gradient in GBM directly as an electronic switch for triggering the in situ chemical rearrangement of hypoxic-

sensitive prodrugs [88,89]. Hua et al. ingeniously developed actively targeted hypoxia-responsive lipid-polymer hybrid NPs [ALP-$(MIs)_n$], providing an innovative strategy for the targeted regulation of the hypoxic microenvironment in immunotherapy [90]. Poly (MIs)n was synthesized via reversible addition–fragmentation transfer polymerization, which was allowed to self-assemble and later loaded with DOX to form hypoxia-responsive NPs [ALP(MIs)n-DOX]. Under hypoxic GBM conditions, the nitro groups within the P-(MIs)n core undergo a single-electron reduction to amine groups, inducing a sharp transition from hydrophobicity to hydrophilicity, structural disassembly, and the rapid release of the encapsulated drug (**Figure 3B**). Under normoxic conditions, ALP-(MIs)n exhibits a distinct absorption peak at 325 nm, which completely disappears under hypoxic conditions, confirming the successful conversion and reduction of internal nitro groups to amino groups within the hypoxic environment (**Figure 3C**). This design translates the physical parameter of hypoxia into a hydrophilic-hydrophobic transition, functioning as a precise unlocking mechanism mediated by a specific biological hypoxia key. This mechanism rapidly disassembles the nanocarrier and achieves a localized burst release of the core drug within 4 h (**Figure 3D**). MIs act as specific radiosensitizers for hypoxic cells by mimicking the effect of oxygen through electron affinity to enhance deoxyribonucleic acid (DNA) damage inflicted by ionizing radiation on hypoxic tumor cells. This action reduces the radiotherapy-resistant cell population and survival of immunosuppressive cells such as MDSCs. Furthermore, encapsulated DOX serves as a potent inducer of immunogenic cell death. Upon precise delivery and high-concentration release within the hypoxic core of GBM, DOX efficiently induces immunogenic cell death in tumor cells, mitigating the severe systemic toxicity associated with the free drug. This process releases substantial amounts of tumor-associated antigens and danger-associated molecular patterns (DAMPs), converting the physicochemical characteristics of the TME into

potent antitumor immune activation signals. This conversion provides an ideal local immune microenvironment for subsequent combination therapies including ICB. Wang et al. recently developed dendritic macromolecular nanogels (DNGs) capable of efficiently crossing the BBB to codeliver immunomodulatory cytokine IFN-γ and specific hypoxia-activated prodrug tirapazamine (TPZ). Nanocarrier-encapsulated TPZ maintains a highly stable, nontoxic, and inert state in oxygen-rich healthy brain tissues, circumventing the systemic off-target toxicity associated with conventional chemotherapeutics [91]. However, these nanocarriers immediately trigger a precise gating mechanism under low partial pressure of oxygen. Hypoxic conditions mediate a single-electron reduction of TPZ to instantaneously convert it into highly cytotoxic free radicals (**Figure 3E**). IFN-γ efficiently drives macrophage polarization toward the antitumor M1 phenotype and significantly elevates the infiltration levels of $CD4^+$ and $CD8^+$ effector T cells within GBM lesions in vivo (**Figure 3F**). This delivery strategy, integrating in situ hypoxia-activated prodrugs with synergistic factor-mediated immune remodeling, demonstrates the translation of GBM-specific hypoxia into a crucial trigger for driving antitumor immunity. Although hypoxia-responsive nanocarriers show a high potential for tumor-targeted drug delivery and combination therapy, the current selection of nanocarriers responsive to pO_2 changes remains limited in GBM treatment. Current research predominantly focuses on developing functional nanocarriers that directly ameliorate the hypoxic TME [92-95]. Hypoxia triggers numerous downstream metabolic remodeling effects, including low pH owing to H^+ accumulation and redox imbalance caused by ROS and GSH accumulation [96].

Although hypoxia-responsive nanocarriers provide an attractive strategy for tumor-selective drug release and tumor microenvironment remodeling, their clinical translation remains constrained by several hypoxia-specific bottlenecks. Tumor hypoxia is highly heterogeneous and

dynamically changes with lesion size, vascular density, disease stage, and therapeutic intervention [97]. As a result, hypoxia-responsive nanocarriers may not achieve consistent activation in tumors with mild, transient, or spatially uneven hypoxia. Severely hypoxic regions are usually poorly perfused, which creates a delivery paradox: nanocarriers rely on blood circulation to enter tumors, whereas the most hypoxic compartments often have the weakest vascular access and limited tissue penetration. This mismatch may reduce nanocarrier accumulation in the regions where hypoxia-triggered activation is expected. In addition, many hypoxia-responsive systems do not directly sense oxygen tension, but instead rely on reductive activation of azo bonds, nitroimidazole groups, quinone structures, or hypoxia-activated prodrug motifs [98]. Their responsiveness is therefore affected by local oxygen gradients, reductase expression, intracellular electron donors, and nanocarrier uptake, which may lead to variable drug release and therapeutic outcomes. Potential off-target activation in non-malignant hypoxic tissues, unclear long-term biosafety, complex pharmacokinetics, and difficulties in scalable and reproducible manufacturing further restrict clinical translation. From the perspective of translational medicine, the future hypoxia-responsive nanocarriers can be combined with hypoxia imaging to optimize the penetration performance of deep tumors. These improvements will help bridge the gap between the promising preclinical efficacy and actual clinical application.

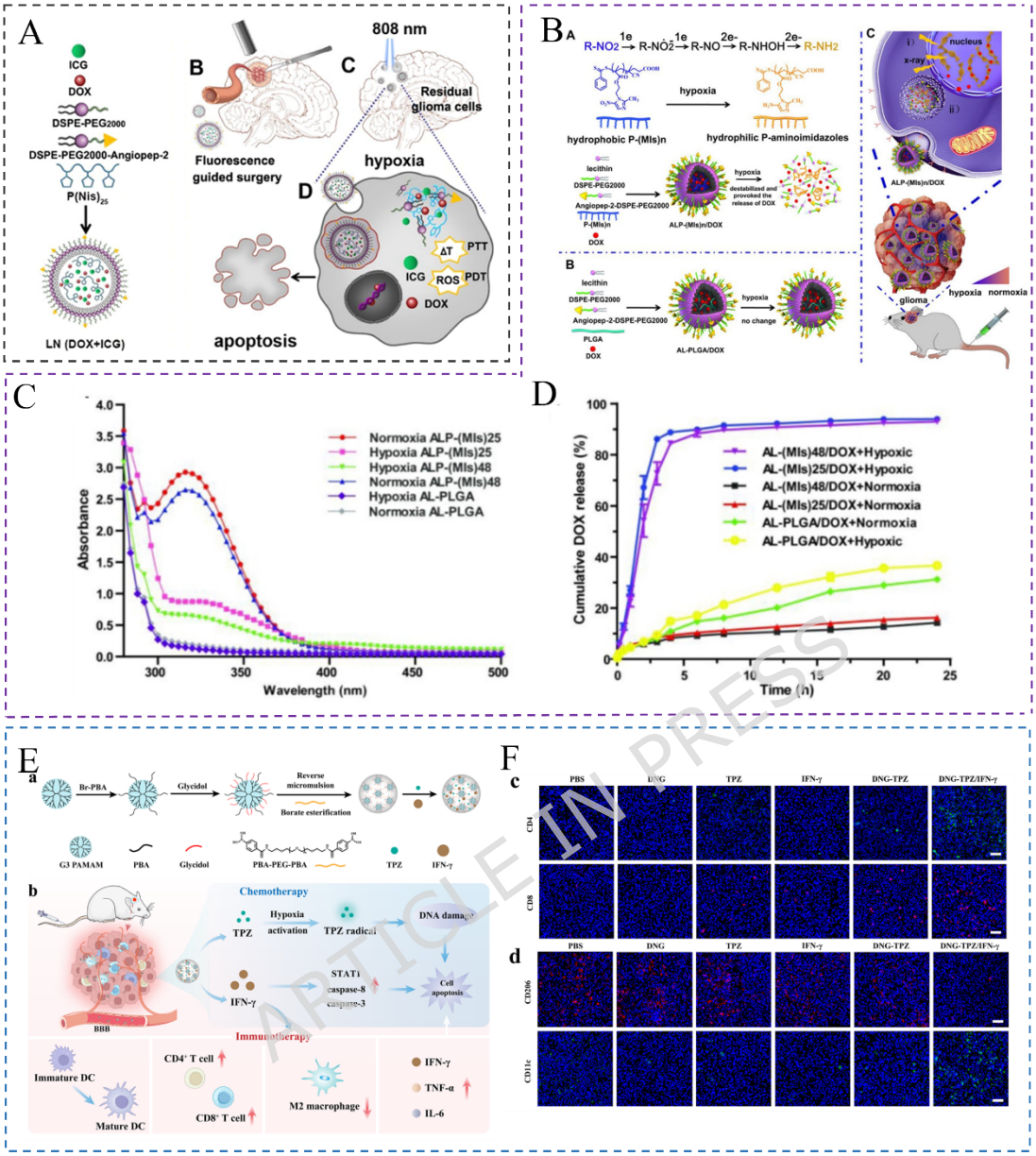


Figure 3. Hypoxia-responsive nanocarriers for GBM immunotherapy. (A) Schematic illustration of the mechanism underlying hypoxia-responsive nanocarrier LN (DOX + ICG)-mediated fluorescence-guided surgery and multimodal synergistic therapy for glioma. Reprinted with permission from Ref. [87]. Copyright 2020 American Chemical Society. License No. 6285921241834. (B)Schematic representation of the construction and anti-glioma mechanism of the hypoxia-responsive and hypoxia-radiosensitizing nanocarrier delivery system, ALP-(MIs)n/DOX. (C)Variations in the absorption spectra of ALP-(MIs)25, ALP-(MIs)48, and control AL-PLGA nanocarriers after incubation under normoxic and hypoxic conditions for 2 h. (D)Drug release profiles of ALP-(MIs)25/DOX, ALP-(MIs)48/DOX, and control AL-PLGA/DOX under normoxia and hypoxia conditions.

Panels B-D reproduced from Ref. [90], available under CC BY-NC 4.0. Copyright 2018, Ivyspring International Publisher. (E) Schematic illustration of the construction process of DNGs-TPZ/IFN-γ and its mechanism for synergistic chemo-immunotherapy of orthotopic glioma. (F) Infiltration levels of $CD4^+$ and $CD8^+$ T cells within the mouse brain tumor tissues, and the expression of M2-type tumor-associated macrophages (TAMs) at the tumor site. Panels E and F are reprinted with permission from Ref. [91]. Copyright 2025, Elsevier. License No. 6285940837969.

5. pH-response

Driven by the Warburg effect, GBM cells heavily rely on glycolysis for energy supply even under aerobic conditions, resulting in the substantial local accumulation of acidic metabolites such as lactate [99]. This unique metabolic reprogramming shapes a slightly acidic TME (pH = 6.5-6.8), in contrast to the physiological pH of 7.4 in normal brain tissue, and establishes a steep pH gradient of 5.0-6.0 within intracellular endosomes and lysosomes [100]. This significant change in the proton concentration provides a precise endogenous trigger for smart delivery systems to induce physicochemical transitions in pH-responsive drug carriers and trigger the cleavage of acid-sensitive bonds. These processes facilitate the release of immunotherapeutic agents and immune remodeling of the microenvironment. The synthesis of pH-responsive nanocarriers primarily relies on three strategies: (i) the introduction of acid-labile chemical bonds, (ii) protonation-driven charge reversal, and (iii) protonation-induced conformational changes (**Table 1**).

5.1 Acid-labile Bonds

Acid-sensitive covalent bonds have been introduced into the backbone structure or drug-binding sites of nanocarriers such as imine [101-103], imines [104], coordinate [105], and *cis*-aconityl bonds [106]. These bonds are highly stable under normal blood circulation conditions; however, upon exposure to a slightly acidic environment, these acid-sensitive bonds rapidly undergo hydrolysis and cleavage, disintegrating the nanocarrier and controlled release of the drug.

The cleavage of acid-labile chemical bonds enables precise and targeted release of immunomodulatory antibodies or drugs within the TME, directly breaching the dual physical and immune barriers of GBM. Introducing acid-sensitive benzoic–imine bonds to link anti-OPN (aOPN) antibodies within a hybrid cell membrane nanocarrier, a prokaryotic–eukaryotic hybrid membrane (HM) multimodal biomimetic nanocarrier FBFO@HM@aOPN was fabricated [107]. In the acidic TME of GBM, high proton concentrations rapidly induce the hydrolysis of the benzoic–imine bond to precisely trigger the in situ detachment of the aOPN antibodies. The released antibodies block the OPN signaling pathway to remodel tumor vasculature and the extracellular matrix (ECM). This remodeling increases vascular permeability and reduces tissue stiffness, promoting deep infiltration of NPs and immune cells. The HM, formed by M1 macrophage exosomes and *Escherichia coli* -derived outer membrane vesicles, endows the platform with highly effective active targeting capabilities against tumor cells and TAMs. As innate immune adjuvants, outer membrane vesicles (OMVs) and ROS, generated by FBFO, jointly activate the Nuclear Factor κ–light-chain-enhancer of activated B cells and cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS-STING) signaling pathways. This activation drives the polarization of M0 macrophages toward the M1 phenotype while simultaneously reprogramming immunosuppressive M2 macrophages into the antitumor M1 state. The nanocarriers induce ferroptosis in tumor cells to provide antigen-presenting cells with abundant tumor-specific neoantigens. Concurrently, it repolarizes TAMs to enhance their antigen presentation and phagocytosis. These combined effects activate innate and adaptive antitumor immunity to effectively inhibit the malignant progression of GBM (**Figure 4A**).

Hydrazone bonds act as classic acid-labile covalent linkages and are frequently used for the direct conjugation of chemotherapeutic agents (**Figure 4B**). Angiopep-2 (An)-modified gold

(Au)NPs were developed by anchoring DOX onto the AuNP surface via hydrazone bonds [An-polyethylene glycol (PEG)-DOX-AuNPs] [108]. The subsequent pH-gated release of DOX at high concentrations exerts fundamental cytotoxicity and transforms the drug into a potent inducer of immunogenic cell death (ICD). This induction compels tumor cells to release substantial amounts of DAMPs to effectively initiate the antitumor immune cycle. Metal–organic frameworks (MOFs) exhibit cascade amplification of this immune activation effect. The cleavage of coordination bonds within the mildly acidic environment degrades copper (Cu)-MOF nanocarriers to release Cu ions, which specifically trigger cuproptosis and ferroptosis in tumor cells [109]. This form of nonapoptotic cell death releases abundant DAMPs that function as potent immunostimulants, effectively activating dendritic cells and eliciting a durable antitumor T-cell immune response (**Figure 4C**).

The smart deshelling of nanocarriers triggered by chemical bond cleavage serves as a critical mechanism for achieving precise targeting and phenotypic reprogramming of immune cells. TAMs act as primary drivers of immune evasion within the TME. Cascade-targeting nanomicelles were prepared using an acid-sensitive diamino ketal linker [110]. They enter the acidic lysosomes of endothelial cells and cleave the ketone bond, inducing the detachment of the outer targeting peptide to expose the internal mannose receptor-targeting moiety. This deshelling mechanism enables the precise delivery of immunomodulatory agents directly into TAMs. This targeted delivery successfully reprograms these cells from a protumoral M2 phenotype into an M1 phenotype characterized by robust antitumor phagocytic activity, reversing immune resistance (**Figure 4D**). Modifying the PEG coating of small extracellular vesicles with a *cis*-aconityl bond allows PEG to cleave and shed in microacidic tumor regions, restoring target cell uptake of the vesicles [106], providing an effective pathway for subsequent delivery of immunomodulatory substances or

enhanced targeted recognition (**Figure 4E**).

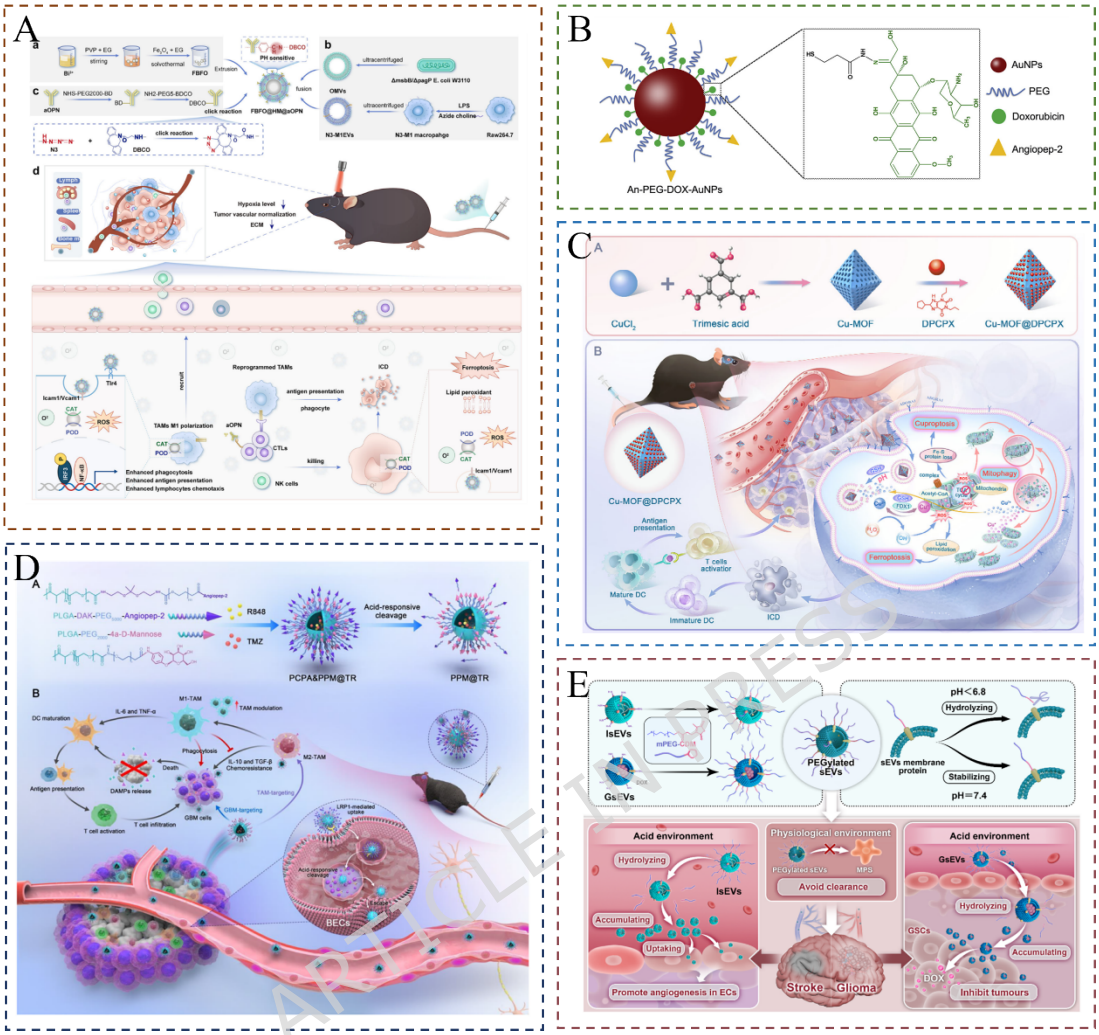


Figure 4. Nanocarriers based on acidic microenvironment-triggered chemical bond cleavage for GBM immunotherapy. (A) Schematic illustration of the design and immunotherapeutic mechanism of a biomimetic intelligent nanocarrier responsive to pH based on benzoic imine linkages. Reproduced from Ref. [107], available under CC BY-NC-ND 4.0. Copyright 2025, The Author(s). (B) Schematic representation of a delivery platform based on hydrazone linkages responsive to pH with dual targeting capabilities and its mechanism for drug release triggered by acidity and targeted delivery within glioblastoma. Reprinted with permission from Ref. [108]. Copyright 2015, Elsevier Ltd. License No. 6285941485993. (C) Schematic illustration of the construction process of the pH-responsive copper-based nanocarrier, Cu-MOF@DPCPX, and its mechanism for inducing cell death via three pathways and facilitating robust immune microenvironment remodeling. Reprinted with

permission from Ref. [109]. Copyright 2025, John Wiley and Sons. License No. 6285960835194. (D) Schematic illustration of the mechanism of pH-responsive hierarchical brain-targeted delivery of PCPA&PPM@TR and the targeted modulation of TAMs for combined chemo-immunotherapy of orthotopic GBM. Reprinted with permission from Ref. [110]. Copyright 2024, Elsevier Ltd. License No. 6285991500562. (E) Schematic illustration of the cascade immune remodeling mechanism mediated by engineered small extracellular vesicles (sEVs) modified with a pH-responsive PEG coating, involving mild acidity-triggered coating dissociation, targeted drug release, and the elicitation of ICD. Reproduced from Ref. [106], available under CC BY-NC-ND 4.0. Copyright 2025, Elsevier Ltd.

5.2 Charge Reversal

Charge-reversal mediated pH-responsive NPs are a class of smart nanocarriers capable of altering their surface charge properties in response to environmental pH fluctuations [111]. Zwitterionic polymeric micelles, PCL-PSDMA, prepared using sulfamethazine, maintain a zwitterionic state within the physiological blood environment, which effectively prolongs circulation time and evades nonspecific clearance by the immune system. Upon encountering the characteristic acidic microenvironment of GBM, the sulfamethazine groups are protonated, and the micelles are positively charged [112]. This in situ generation of positive charge substantially enhances the electrostatic affinity between the NPs and tumor tissues to promote effective drug accumulation and deep penetration within the GBM. This charge-switching property improves drug delivery efficiency and overcomes biological barriers, enhancing the efficacy of combined chemo-immunotherapy against GBM (**Figure 5A**). In addition to promoting cellular uptake, this charge-reversal mechanism can precisely release immunotherapeutic drugs into the ECM by controlling carrier disintegration, preventing targeting failure. Lin et al. reported a nanocarrier system (PCNPs), featuring a polyhistidine core and phosphatidylcholine shell, to modulate the immunosuppressive microenvironment of GBM [113]. This carrier remains electrically neutral at

physiological pH and penetrates the BBB via choline transporters. Upon reaching the GBM, the PHIS core undergoes protonation, and the resulting strong electrostatic repulsion directly triggers the disassembly of the entire nanostructure to achieve extracellular drug release. Codelivering TMZ and the adenosine receptor antagonist CPI-444, this strategy induces ICD and blocks the critical adenosine-A2AR immunosuppressive pathway in the TME. This combination effectively reverses the local immune tolerance state of GBM (**Figure 5B**). Advanced pH-responsive nanocarriers exploit acid-degradation properties to achieve precise and differential interventions across diverse cell populations within the tumor, facilitating the cascade amplification of immune responses. A microenvironment-responsive nanoagonist, formulated by conjugating the organic polymer PC6AB with an inorganic manganese phosphate oligomer, exhibited spatiotemporally coordinated intervention in GBM immune pathways [114]. Triggered by the acidic TME, this nanostimulant specifically degraded into two active components comprising PC6AB and the manganese phosphate oligomer. PC6AB exhibited membrane-disrupting activity to selectively target tumor cells, effectively inducing ICD and releasing tumor antigens. Concurrently, immune cells such as microglia absorbed inorganic manganese (Mn), directly activating the intracellular STING pathway to trigger potent downstream immunostimulatory signals. This mechanism achieves spatiotemporally differential delivery to tumor and immune cells (**Figure 5C**).

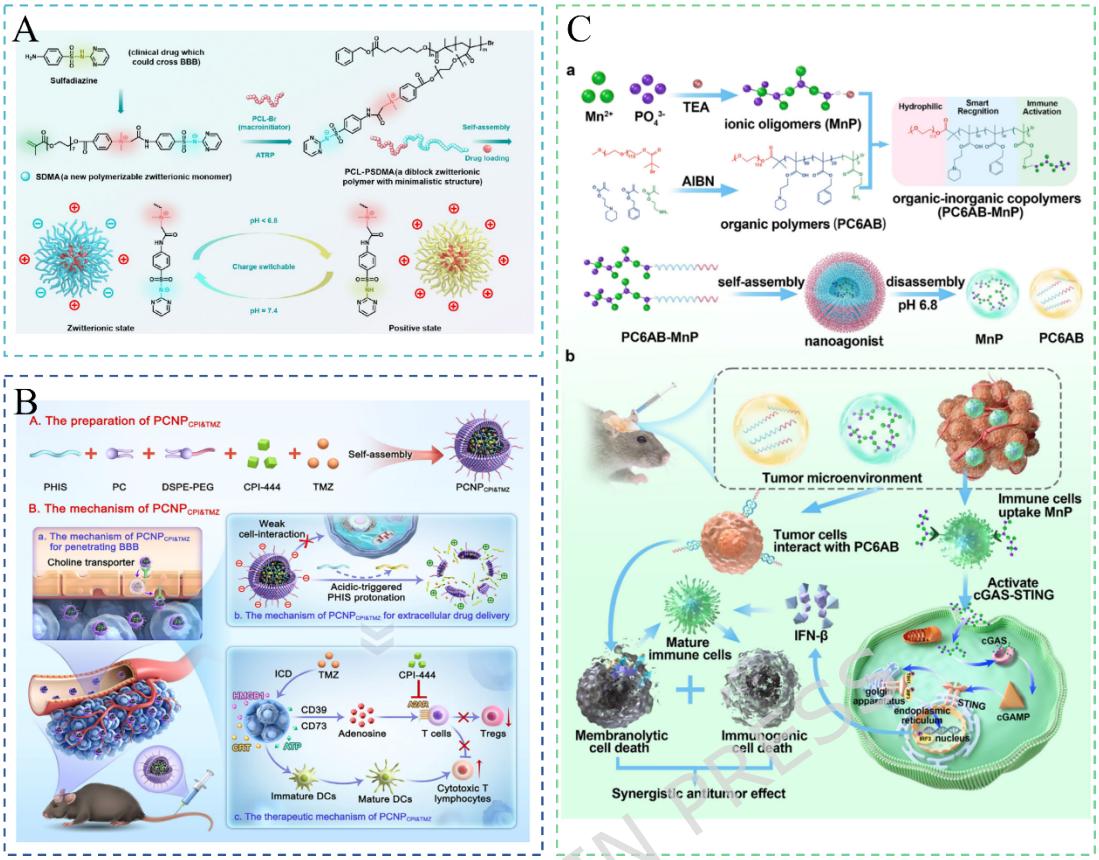


Figure 5. pH-responsive nanocarriers based on charge reversal for GBM immunotherapy. (A) Synthesis of a novel zwitterionic SDMA monomer and diblock PCL-PSDMA micelles endowed with smart charge-conversion capability. Reprinted with permission from Ref. [112]. Copyright 2025, American Chemical Society. License No. 6286391037531. (B) Schematic illustration of the design and mechanism of PC-modified pH-responsive charge-reversal nanocarriers. These nanocarriers undergo protonation-induced disassembly and drug release within the acidic glioma microenvironment to synergistically induce ICD, block the adenosine-A2AR pathway, reverse the immunosuppressive microenvironment, and activate anti-tumor immunity. Reprinted with permission from Ref. [113]. Copyright 2025, Wiley-VCH GmbH. License No. 6286420074080. (C) Schematic illustration of organic-inorganic copolymer nanoagonists that undergo charge reversal and disassembly in response to the mildly acidic GBM microenvironment, synergistically enhancing anti-tumor immune responses via the specific disruption of tumor cell membranes and the release of MnP to activate immune cell pathways. Reproduced from Ref. [114] , available under CC BY-NC-ND 4.0. Copyright 2025, The Author(s).

5.3 Protonation-Induced Conformational Changes

Protonation-induced conformational alteration represents a highly efficient strategy for designing pH-responsive nanocarriers to enhance tumor immunotherapy. This strategy uses the protonation of specific internal groups within the material to trigger the conformational remodeling of carrier molecules, inducing significant structural changes: polymer chain extension, volume expansion, dissociation, or protein backbone loosening. These changes subsequently enable the precise release of immunomodulatory agents and cytotoxic drugs. Inorganic NPs (such as calcium carbonate and calcium phosphate) with certain acid-sensitive moieties (including amide bonds [115] and the imidazole ring of histidine [116,117]) undergo protonation within the acidic tumor environment, altering the structure and function of the self-assembled NPs.

In synthetic polymeric nanocarriers, protonation frequently triggers a hydrophobic-to-hydrophilic phase transition within the polymer to induce the extension or expansion of the nanocarrier conformation. The conformational shift toward a hydrophilic extended state enables the effective exposure of internal cryptic functional groups. Poly (2-hexamethyleneiminoethyl methacrylate) NPs (AMD@iNP_DBCO) maintain a highly contracted state under neutral physiological conditions. Triggered by the mildly acidic TME, their tertiary amine groups undergo rapid protonation and transition to a hydrophilic state. Thus, the polymer chains extend and expose the reactive groups, which undergo a bioorthogonal reaction with another nanocarrier system CPI@iNP_N3 [118]. This in situ assembly, initiated by conformational changes, significantly prolongs the extracellular retention time of drugs within the tumor and synergistically induces ICD (**Figure 6A**). The volume expansion caused by protonation amplifies the synergistic effects of external physical therapies. On protonation in a mildly acidic environment, the core hydration of smart nanoprobes (BEAGA/ApoE-PDHD) containing multiple amino groups drastically expands the nanocarrier volume. During this process, the particle size increases from 210 nm to 575 nm,

promoting water absorption and substantially lowering the vaporization threshold of ultrasound contrast agents [119]. This conformational alteration disrupts the structural stability of the carrier and synergizes with the cavitation effect of low-frequency ultrasound to accelerate drug release. ROS generated by ILD induce ICD in tumor cells, while R848 promotes dendritic cell maturation and recruits the infiltration of $CD8^+$ T cells. The synergistic integration of conformational change, targeted drug release, and robust immune activation profoundly enhances the therapeutic efficacy against GBM (**Figure 6B**).

The FAP-targeted nanocarrier MMAE@FAPtp-HFn, constructed based on human heavy chain ferritin, uses protonation-induced conformational alterations to achieve pH-responsive drug release. In addition to exerting chemotherapeutic effects, MMAE@FAPtp-HFn effectively activates antitumor immunity and remodels the immunosuppressive microenvironment of GBM [120]. The protein nanocage, assembled from 24 subunits, can release its payload slowly and continuously for >24 h under neutral pH conditions. Under acidic conditions, specific amino acid residues at the interfaces of the ferritin subunits rapidly undergo protonation. Changes in local electrostatic interactions cause the protein scaffold to undergo conformational loosening or even partial disassembly, triggering a burst release of MMAE (**Figure 6C**). This responsive release, governed by conformational alterations, precisely eradicates target cells and induces robust ICD, resulting in a highly significant elevation in the local immunogenic cell death score within the treatment group (**Figure 6D**). Stimulated by these potent danger signals, the Type I interferon signaling pathway within the TME undergoes broad activation to significantly upregulate key antitumor chemokines, including CXCL10, and various immune effector genes (**Figure 6E, F**). This activation successfully converts the immunosuppressive state of the GBM into an immune-active phenotype, which substantially prolongs the survival of mice bearing orthotopic tumors.

The application of pH-responsive nanocarriers in tumor-targeted delivery still faces several challenges associated with pH-responsive mechanisms. After systemic administration, nanocarriers sequentially encounter different biological environments, including blood circulation, tumor interstitium, cellular membranes, endosomes, and lysosomes, which differ in acidity, protein composition, residence time, and transport barriers. Therefore, poorly controlled activation timing or activation stage may lead to premature cargo leakage, insufficient deep tumor penetration, lysosomal sequestration, incomplete intracellular release, or reduced drug availability at the intended site of action.

Because the pH of endosomes and lysosomes is generally lower and more stable than extracellular tumor pH, promoting endosomal escape may represent a more feasible near-term translational goal for many pH-sensitive nanocarriers [121]. In addition, charge-reversal or protonation-based pH-responsive systems may enhance cellular uptake, tumor retention, or blood-brain barrier transport [122]; however, acid-triggered cationic surfaces may also increase nonspecific protein adsorption, membrane perturbation, hemolytic risk, endothelial interactions, inflammatory responses, and rapid clearance by the mononuclear phagocyte system. Therefore, future pH-responsive nanocarriers should clearly define their intended activation stage, validate release behavior in serum-containing systems and three-dimensional tumor models, and prioritize reproducible manufacturing, scale-up feasibility, storage stability, biodegradable components, and pharmacokinetic/pharmacodynamic correlations for clinical translation.

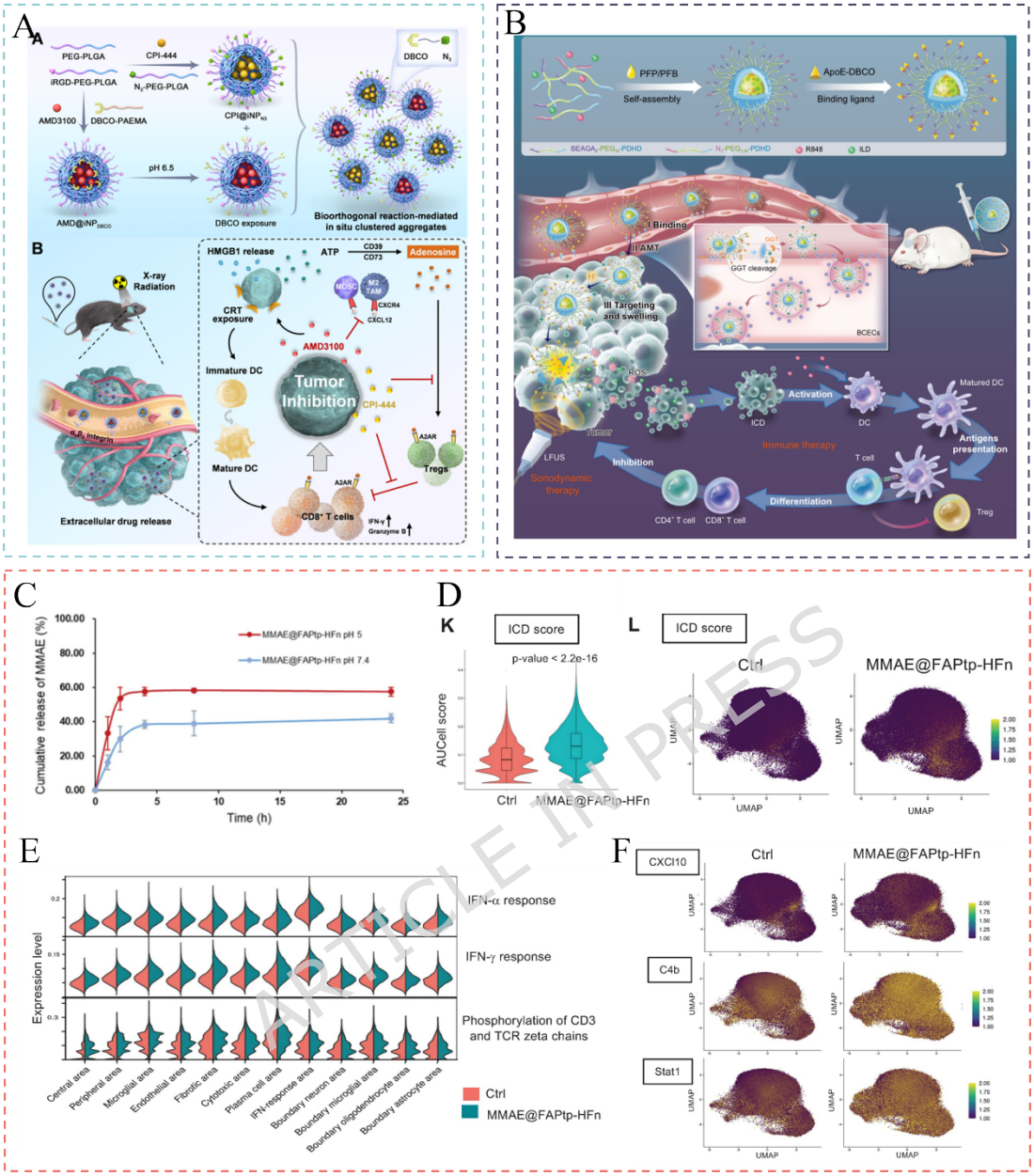


Figure 6. Acid-triggered conformational changes of nanocarriers for GBM immunotherapy. (A) Preparation of an acidity-triggered in situ bioorthogonal assembly nanocarrier and its application in synergistic immunotherapy for GBM via the extracellular targeted blockade of CXCR4 and adenosine. Reprinted with permission from Ref. [118]. Copyright 2025, Elsevier Ltd. License No. 6286421002055. (B) Schematic illustration of the mechanism by which a pH-responsive nanoprobe enhances immune-sonodynamic therapy for GBM through conformational alteration and volume expansion. Reproduced from Ref. [119] , available under CC BY-NC-ND 4.0. Copyright 2024, The Author(s). (C) pH-responsive release profiles of MMAE from FAPtp-

HFn at pH 5 and pH 7. (D) Robust ICD effect elicited by MMAE@FAPtp-HFn at the local tumor site. (E) Enrichment scores of key immune signaling pathways, such as the type I interferon pathway, within the local tumor microenvironment. (F) Spatial expression mapping of critical immune chemokines at the tumor site following treatment with the targeted nanocarriers. Panels C-F reproduced from Ref. [120], available under CC BY-NC 4.0. Copyright 2026, The author(s).

6. Redox Response

However, in GBM cells, this balance shifts toward the profound accumulation of oxidative species, including reactive oxygen and nitrogen species. This shift primarily results from heightened metabolic activity and the increased production of these metabolites by infiltrating immune cells [123]. To counteract this elevated oxidative stress, the intracellular concentrations of reducing agents, such as GSH, concurrently increase. Exploiting these robust ROS and GSH responses serves as a direct and highly effective strategy for inhibiting tumor cells and advancing cancer therapy [124]. Based on the core characteristic of redox homeostasis imbalance in the TME, researchers have designed a large number of ROS- and GSH-responsive NPs to ameliorate the immunosuppressive state of GBM (**Table 2**).

6.1 ROS-responsive Nanocarriers

ROS constitute the primary intracellular oxidative agents, and their excessive accumulation induces irreversible oxidative damage to cells and tissues[125,126]. Compared with normal cells, steady-state ROS levels are elevated in glioma cells owing to the reprogramming of redox metabolism, making tumor cells more susceptible to the effects of further increases in ROS levels than normal cells [127]. Furthermore, nitrogen oxide and ROS generated by tumor-associated myeloid cells suppress T-cells [128]. Thus, the development of ROS-responsive nanocarriers has emerged as a cutting-edge strategy for the precise delivery of immunomodulatory agents and gene therapies to reverse the immunosuppressive microenvironment of GBM [129,130].

The massive infiltration of glioma-associated microglia and macrophages (GAMs) within the GBM microenvironment serves as a core factor driving adaptive immune tolerance [131,132]. Considering the multifunctional properties of bacterial OMVs as natural carriers and immunoadjuvants, attenuated OMVs (ΔmsbB OMVs) were used to design an ROS-responsive cationic polymer (AO@PTP/47aD). This system achieves synergistic loading and precise intracellular release of siCd47 and DOX to concurrently overcome the intrinsic and adaptive immune resistance of GBM [133]. Triggered by the high intracellular ROS concentration in GBM cells, the released DOX overcomes the intrinsic immune resistance by inducing ICD, promoting the maturation of dendritic cells (DCs), and T-cell activation. The immunostimulatory properties of OMVs, released siCd47, and this nanocarrier can simultaneously initiate the reprogramming of GAMs and destroy CD47 in GBM cells to overcome adaptive immune resistance. This enhances antitumor effects (e.g., release of proinflammatory cytokines) and the phagocytosis of GBM cells by GAMs, inhibiting tumor growth in an orthotopic GBM mouse model by inducing a robust antitumor immune response (**Figure 7A**). Although ROS-responsive codelivery strategies for genes and immunomodulators show immense potential in remodeling the TME, biological macromolecules [e.g., siRNA or clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (CRISPR-Cas9)] are highly susceptible to degradation during circulation across the BBB. Preventing their premature release in nontarget regions and ensuring their precise entry into the cytoplasm of tumor cells remain formidable challenges, limiting their clinical translation. To address the safety and precision of macromolecular delivery, Zhao et al. developed an innovative polymer-locked fusogenic liposome (Plofsome) [134]. This system uses a traceless ROS-cleavable linker to anchor four-arm PEG–*ortho*-diphenol (4-arm PEG-*o*DP) onto (An)-modified fusogenic liposomes, functioning as a safety lock for membrane fusion. Upon

entering the high-ROS microenvironment within the GBM tissue, 4-arm PEG-*o*DP detaches, exposing the fusogenic activity of liposomes and subsequently releasing siMDK or CRISPR-Cas9 ribonucleoprotein (RNP) complexes. This ROS-regulated membrane fusion mechanism reduces off-target toxicity and successfully delivers siRNA or the CRISPR-Cas9 ribonucleoprotein complex directly and safely into the cytoplasm of target cells. Plofsome@siMDK combined with TMZ treatment significantly elevates the levels of the DNA damage marker gamma histone (γ-H2AX) in tumor tissues. This elevation demonstrates the successful reversal of TMZ resistance, restoring the TMZ-induced ICD effect and indirectly activating the in vivo antitumor immune response. However, the vast differences in molecular weights and surface charges between Cas9 and single guide (sg)RNA render the site-specific delivery of Cas9/sgRNA, a major obstacle in CRISPR/Cas9 gene therapy, imposing contradictory demands on the carrier. To achieve efficient intracellular delivery of RNP, a cationic ROS-responsive phenylboronic acid–branched polymer (CRP) was synthesized, which could electrostatically concentrate sgSTAT3 in the inner compartment and coordinate the repair of Cas9 in the outer compartment. The resulting nanocomplexes were further hybridized with liposomes modified with the 4F-An fusogenic peptide to yield the final hybrid NPs (^{Cas9}ARLP/sgSTAT3) [135]. Under the influence of the high ROS concentration in glioma, CRP undergoes deboronation and charge elimination to form an electroneutral zwitterionic polymer, which ceases to interact with the negatively charged sgSTAT3 or positively charged Cas9, facilitating their rapid release. Through its ingenious compartmentalized loading and ROS-responsive design, these lipid–polymer hybrid NPs exhibit precise delivery and controlled release of CRISPR-Cas9 at the GBM site. Eliminating STAT3 to downregulate vascular EGF expression, it exhibits tumor vascular normalization and immune cell infiltration within the microenvironment (**Figure 7B**). This ROS-responsive hybrid nanocarrier-

mediated localized delivery of Cas9 and sgRNA offers a potential strategy for genome editing in GBM therapy. In addition to using the charge-neutralization mechanism of phenylboronic acid, Zheng et al. developed an ROS-responsive polymeric siRNA nanocarrier (Ang-3I-NM@siRNA) stabilized via triple interactions [136]. Based on traditional electrostatic binding, this system incorporates hydrogen bonding and hydrophobic interactions provided by phenylboronic esters, endowing the nanocarrier with exceptional stability in the bloodstream. The targeting peptide-modified nanocarrier penetrates GBM tissue with high ROS concentrations. The hydrophobic phenylboronic acid esters undergo specific oxidative cleavage, converting into hydrophilic carboxyl groups. This precise hydrophobic-to-hydrophilic transition directly dismantles the hydrophobic stabilizing forces and causes the newly generated carboxyl groups to trigger internal competition for electrostatic and hydrogen bonds. Thus, cascade disintegration of multiple stabilization mechanisms is caused, with the targeted release of siRNA (**Figure 7C**). This gene delivery strategy, which leverages the variable responses of ROS to various chemical bonds, exhibits the normalization of GBM tumor vasculature for subsequently overcoming the physical barriers that prevent antitumor immune cells from infiltrating deep into the tumor.

Given the heterogeneity of endogenous ROS distribution within solid tumors, amplifying ROS signals via exogenous stimulation can further enhance systemic immune responses. Kang et al. designed an ultrasound-responsive nanocarrier, SeM@GL NPs [137]. This platform uses a novel selenium-containing compound to produce a potent sonodynamic therapy effect under ultrasound irradiation, which induces the massive generation of ROS. These abundantly generated ROS directly induce ICD in tumor cells and function as an internal secondary trigger switch. This switch specifically initiates the self-accelerating cleavage and release of a coassembled STING agonist prodrug featuring a diselenide bond within the nanocarrier. The released agonist effectively

activates the cGAS-STING pathway in dendritic cells to promote their maturation and antigen cross presentation, efficiently driving the proliferation and infiltration of tumor-specific $CD8^+$ T cells. A CXCR4-blocking peptide conjugated to the carrier surface effectively inhibits the infiltration pathways of immunosuppressive cells. This combined approach successfully converts GBM from an immunologically cold tumor into a hot tumor (**Figure 7D**).

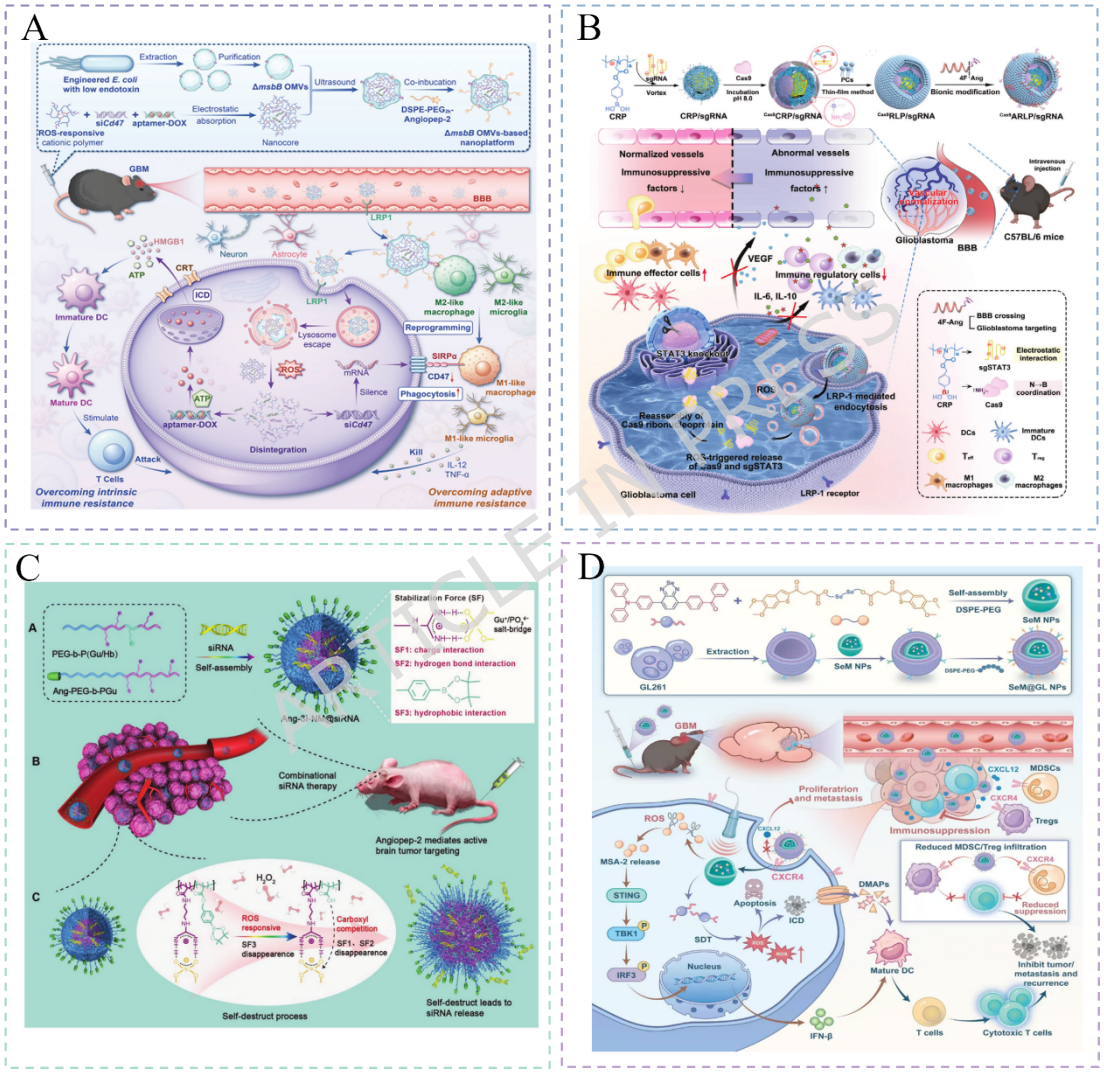


Figure 7. ROS-responsive nanocarriers for enhancing GBM immunotherapy. (A) Synthesis of the ROS-responsive nanocarrier AO@PTP/47aD and its mechanism for enhancing GBM immunotherapy by overcoming dual immune tolerance. Reprinted with permission from Ref. [133]. Copyright 2025, Wiley-VCH GmbH. License No. 6286440642109. (B) Schematic illustration of the construction of the ROS-responsive nanocarrier

^{Cas9}ARLP/sgRNA and its mechanism for enhancing GBM immunotherapy via CRISPR/Cas9 genome editing-mediated vascular and immune reprogramming. Reproduced from Ref. [135], available under CC BY-NC-ND 4.0. Copyright 2024, The Author(s). (C) Schematic illustration of the construction, responsive mechanism, and GBM-targeted combination RNAi therapy of a "triple-interaction"-stabilized ROS-responsive siRNA nanocarrier (Ang-3I-NM@siRNA). Reprinted with permission from Ref. [136]. Copyright 2019, Wiley-VCH GmbH. License No. 6286460338398. (D) Schematic illustration of the construction and ROS-responsive mechanism of an ultrasound-responsive nanocarrier, alongside its mechanism for enhancing GBM immunotherapy by synergistically overcoming immune tolerance through multiple pathways. Reprinted with permission from Ref. [137]. Copyright 2025, Wiley-VCH GmbH. License No. 6286460543983.

6.2 GSH-Responsive Nanocarriers

Responsive nanocarriers designed specifically for the high GSH microenvironment of glioma enable on-demand synergistic chemotherapy and PDT (Chemo-PDT) guided by dual-modal magnetic resonance and fluorescence imaging in orthotopic models [138]. Their capacity for GSH-responsive drug release effectively activates the antitumor immune response, achieving synergistic immunotherapeutic efficacy against GBM. The prevalent strategy for developing GSH-responsive NPs is incorporating disulfide bonds into the material structure, rendering them highly sensitive to GSH-mediated reduction reactions [139-142] .

Through the specific cleavage of disulfide bonds, GSH-responsive NPs can achieve the synchronized, targeted release of chemotherapeutics and immune checkpoint inhibitors, initiating immune remodeling via the ICD effect. Zhang et al. constructed An-modified redox-responsive nanomicelles A2-APM. The core design of this system relies on using a disulfide-containing crosslinker to coencapsulate aPD-L1 and paclitaxel (PTX) within a PEG-poly(L-lysine) (PLL) polymer [143]. Following the An-mediated penetration of the blood-tumor barrier, the high GSH concentration within the TME exclusively triggers the reductive cleavage of disulfide bonds. This cleavage causes the disassembly of the micellar structure and the synchronized release of aPD-L1

and PTX. The rapidly released PTX exhibits excellent inhibitory properties against GBM cells and facilitates ICB therapy by inducing ICD, which sensitizes the tumor to PD-1/PD-L1 blockade (**Figure 8A**). Huang et al. designed a responsive nanogel vaccine based on disulfide crosslinking, which used the elevated intracellular GSH levels in GBM to trigger the rapid degradation of the material structure, exhibiting the spatiotemporally synchronized release of chemotherapeutics and immune-enhancing components [144]. This controlled release profile enhanced ROS-based cytotoxicity and established an in situ immune-activating microenvironment by efficiently inducing ICD and the recruitment and maturation of DCs (**Figure 8B**).

Beyond inducing antigen exposure, GSH-responsive nanocarriers can reverse GBM immune evasion via the precise delivery of functional elements. Zhou et al. reported a GSH-sensitive nano-interferer (OMV@HM-T/F) [145]. Upon entering the lesion, this system responds to local redox signals to release metabolic regulators. Blocking sialylation metabolism on the glioblastoma cell surface, OMV@HM-T/F effectively attenuates the immune steric hindrance mediated by aberrant glycosylation, enhancing the recognition of tumor antigens and the subsequent infiltration by immune cells (**Figure 8C**). Similarly, Zou et al. engineered GSH-sensitive, disulfide-coated CRISPR-Cas9 nanocarriers to design a noninvasive brain delivery system ANP_{SS}[Cas9/sg growth differentiation factor 15 (GDF15)] [146]. This platform releases gene-editing tools by exploiting the GSH-triggered intracellular deshelling effect. Selectively eliminating the immunosuppressive factor GDF15, this approach fundamentally reverses the suppressive attributes of the TME at the genetic level (**Figure 8D**).

Several highly innovative NPs ingeniously integrate two key strategies of GSH responsiveness: (i) they precisely trigger the targeted release of therapeutic agents by cleaving specific disulfide bonds within a high-GSH environment, and (ii) they actively deplete GSH via

redox reactions to profoundly remodel the glioma microenvironment, effectively dismantling the defensive barriers of tumor cells [139,142]. The fusion of GSH-responsive mechanisms with biomimetic technologies elevates immune remodeling to a systemic chemotactic cascade. Fan et al. combined a manganese porphyrin derivative (MnP) with bovine serum albumin (BSA) via self-assembly to form MnP-BSA core NPs, which were conjugated to anti-PD-1 antibodies (aPD-1) via disulfide bonds. The resulting MnP-BSA-aPD-1 NPs were coated with microglia membranes, endowing them with the capability to penetrate the BBB [147]. In a high-GSH microenvironment, the disulfide bond between aPD-1 and MnP-BSA breaks, causing the NPs to disintegrate. Mn^{3+} in MnP is reduced to Mn^{2+} by GSH. The released Mn ions act as potent immunostimulants, capable of activating the cGAS-STING signaling pathway in situ. Inducing the production of Type I IFN, they reshape the chemokine profile, mediating the massive recruitment and infiltration of $CD8^+$ T cells into GBM tissue. In response to near-infrared laser irradiation, the porphyrin directly ablates the tumor and induces ICD. This releases tumor-associated antigens and DAMPs, promoting DC maturation, $CD8^+$ T-cell infiltration, and the antitumor immune response. Moreover, the integration of biomimetic NPs with antiPD-1 antibodies blocks the PD-1/PD-L1 signaling axis, inhibiting immune evasion and synergistically upregulating the antitumor response (**Figure 8E**). These innovative NPs integrate the dual advantages of triggered drug release and GSH depletion. Through the synergistic effect of photothermal therapy, they effectively enhance the antitumor immune response, dismantle tumor immune evasion, and improve therapeutic targeting, opening a novel avenue for the effective treatment of GBM.

The dilemma between systemic circulation stability and redox sensitivity represents a primary challenge for the clinical translation of redox-responsive nanocarriers. Disulfide-, diselenide-, thioether-, and redox-sensitive coordination-based nanocarriers are expected to remain stable

during blood circulation while rapidly releasing their payloads in the reductive tumor microenvironment or after tumor cell internalization. However, if redox-labile bonds are designed to be overly sensitive, they may undergo premature cleavage or thiol-disulfide exchange during circulation under the influence of free thiols in serum proteins, low-abundance reducing species, or nonspecific interactions with biological components, leading to cargo leakage, reduced tumor-targeted accumulation, and increased systemic toxicity. Conversely, if the responsive structures are too stable, nanocarriers may degrade slowly or incompletely after tumor cell internalization, resulting in insufficient intracellular drug release and failure to reach effective therapeutic concentrations [148]. Therefore, future redox-responsive nanocarriers should not simply pursue higher response sensitivity; instead, they should define appropriate activation thresholds and achieve a balance between circulation stability and rapid intracellular release.

The current research frontier has advanced beyond single-responsive strategies. Several multifunctional synergistic nanocarriers have been designed for responding to specific signals within the TME for smart drug release and actively regulating and remodeling the microenvironment itself, such as by integrating pH-responsive capabilities with hypoxia-ameliorating functions. This integrated response-regulation strategy represents the future trajectory of nanocarriers in glioma therapy, aiming to achieve the precise, dynamic, and comprehensive remodeling of the TME.

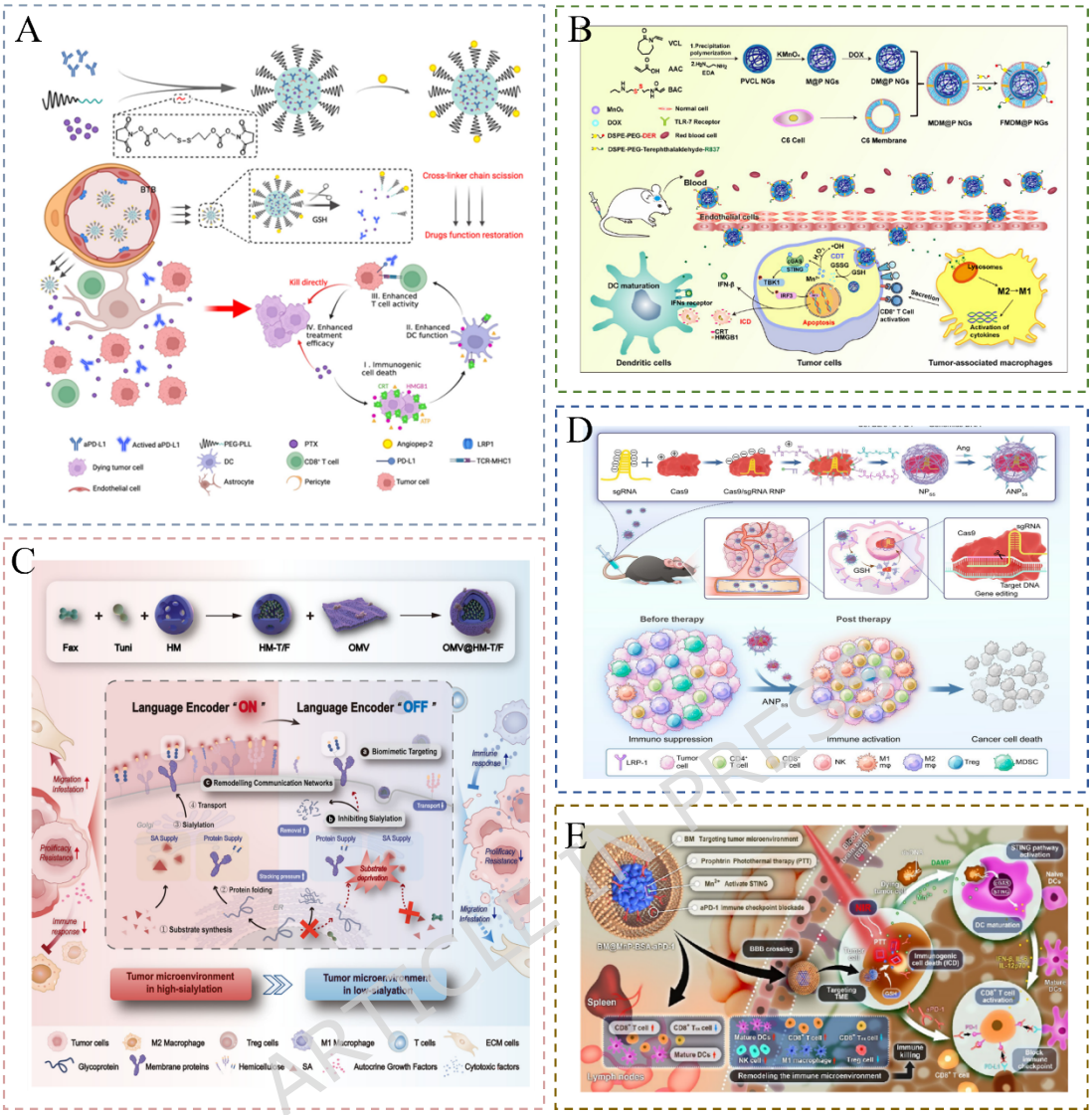


Figure 8. GSH-responsive nanocarriers for enhancing GBM immunotherapy. (A) Schematic of GSH-sensitive A2-APM nanomicelles undergoing disulfide bond cleavage and dissociation in a high-GSH environment, enabling the targeted release of aPD-L1 and PTX for combined chemo-immunotherapy. Reproduced from Ref. [143] , available under CC BY-NC-ND 4.0. Copyright 2024, The Author(s). (B) GSH-triggered disulfide bond cleavage within FMDM@P nanogels (NGs) for the release of encapsulated MnO2, DOX, and R837 to potentiate the immune response. Reprinted with permission from Ref. [144]. Copyright 2024 American Chemical Society. License No. 6286461321316. (C) Schematic illustration of the construction of a redox-responsive nanodisturber and its mechanism for remodeling the GBM immune microenvironment via the modulation of sialylation metabolism. Reprinted with permission from Ref. [145]. Copyright 2025, Wiley-VCH

GmbH. License No. 6286470031368. (D) Disassembly of responsive ANPSS(Cas9/sgGDF15) nanocarriers in GSH-enriched regions for the targeted release of Cas9 and sgGDF15, leading to tumor growth inhibition and the remodeling of the GBM immune microenvironment. Reproduced from Ref. [146] , available under CC BY-NC-ND 4.0. Copyright 2025, The Author(s). (E) Cleavage of disulfide bonds between aPD-1 and MnP-BSA within a GSH-rich microenvironment, triggering the disassembly of MnP-BSA-aPD-1 nanocarriers to amplify the anti-tumor immune response. Reproduced from Ref. [147] , available under CC BY-NC-ND 4.0. Copyright 2024, American Chemical Society.

7. Multi-response Synergistic Strategy

Although single-responsive nanocarriers have ameliorated certain limitations in drug delivery, single stimulus–responsive therapeutic strategies face fundamental constraints when confronting the high heterogeneity and dynamic evolutionary characteristics of the GBM microenvironment [149,150]. A promising approach to enhancing the tumor selectivity of responsive nanocarriers involves developing systems that require the colocalization of multiple stimuli to activate drug release. Integrating various responsive strategies would enable the design of multi-responsive immunotherapeutic nanocarriers. These advanced systems achieve the precise targeting and effective accumulation of therapeutic agents at the tumor site, improving their immunotherapeutic efficacy (**Table 3**) [151].

Among the reported stimulus-responsive GBM therapeutic strategies, the pH–GSH dual-responsive design is an extensively studied approach [152-154]. The acidic microenvironment at the GBM site, combined with high GSH concentrations, constitutes a dual-specific signal that can disrupt the nanocarrier structure or activate prodrug molecules, enabling the synergistic delivery and precise release of immunomodulators and chemotherapeutic agents. GCNPs [151] and M@TP [155] use the acidic microenvironment to facilitate the crucial endosomal escape of carriers. High intracellular GSH levels reduce disulfide bonds within the structure, resulting in the burst release

of the active payload. Leveraging this mechanism, the GCNP system releases a CRISPR/Cas9 system in situ to target and eliminate the PD-L1 gene. This strategy effectively silences PD-L1 expression, restores T-cell activity, and synergizes with TMZ to significantly enhance $CD8^+$ T-cell infiltration and proinflammatory cytokine secretion, substantially prolonging the survival of mice in the GBM model. It provides a safe and efficient delivery platform for gene editing–mediated immunotherapy. M@TP, a biomimetic hybrid proteolysis-targeting chimera (PROTAC)-based nanovesicle, exhibits BBB penetration and homotargeting by mimicking the tumor cell membrane. Under acidic conditions inside tumor cells, the protonation of pH-sensitive amino acid residues in membrane-associated proteins disrupts the vesicle structure, promoting the release of TMZ and the PROTAC prodrug (PC-ss-Pro). The high intratumoral GSH concentration specifically cleaves the disulfide bond within the prodrug, activating the PROTAC molecule to degrade the BRD4 protein. While restoring cellular sensitivity to chemotherapy, this process synergistically dismantles the tumor immune barrier by inhibiting resistance-associated immunosuppressive signals. Cu-MOF@DPCPX nanocomposite integrates a pH/GSH dual response with a metal ion–mediated cell death mechanism to profoundly remodel the immune microenvironment [109]. This pH-triggered release and GSH-triggered activation dual-responsive strategy minimizes the nonspecific release and activation of drugs in normal tissues, enhancing therapeutic efficacy and reducing toxic side effects.

In addition to the classic pH/GSH dual-responsive mechanism, researchers further introduced a protease-responsive mechanism to address the high density of the ECM in GBM tissue and the resulting delivery barriers, enabling deep tumor penetration and in situ immune remodeling. Li et al. developed an MMP-2 and GSH dual-responsive peptide-drug conjugate self-assembling nanocarrier (^{MA}PDCs) to achieve the cascade remodeling of the immune GBM microenvironment

[156]. This system initially utilizes the highly expressed MMP-2 enzyme as a first-stage switch to specifically cleave the surface-modified peptide segments. This enhances deep penetration and retention of drugs within tumor tissues and establishes the necessary conditions for subsequent intracellular responses. Upon entering tumor cells or TAMs, the high intracellular GSH concentration acts as a second-stage switch, rapidly cleaving the disulfide-linked arms and triggering the explosive release of the chemotherapeutic drug camptothecin and R848. This strategy effectively repolarizes GAMs from the protumoral M2 phenotype to the antitumoral M1 phenotype, profoundly coupling chemotherapeutic toxicity with immune reactivation. Similarly, the dual-NP system uses an MMP-2/pH dual-sensitive linker. It uses enzyme-triggered carrier disassembly to enable the deep diffusion of small-sized NPs and leverages the acidic environment to induce the in situ formation of a nanogel [157]. This dynamic switching of physical states significantly prolongs the chemotherapy-induced ICD effect, continuously releasing DAMPs to activate DCs, providing a time-dependent boost for the immunological reactivation of cold tumors.

Integrating pH and ROS responsiveness has also emerged as a potent strategy for enhancing GBM immunotherapy. DNGs were prepared using partially phenylboronic acid–modified dendrimers. Their core boronate ester bonds exhibited sensitive pH/ROS-triggered degradation properties [157]. Synergistically triggered by the acidic environment and high ROS levels within GBM, the nanogels undergo a collapse-like disassembly to synchronously release the hypoxia-activated prodrug TPZ and immune cytokine IFN-γ. This design leverages the immunogenic effects generated by TPZ in hypoxic regions to compensate for the blind spots of conventional immunotherapy while directly reversing immunosuppression via IFN-γ. This process exhibits a cascade closed-loop encompassing chemotherapy, hypoxia sensitization, and immune defense. These multi-responsive synergistic strategies enable more precisely controlled drug delivery from

macroscopic tissue penetration to microscopic molecular activation through the coordinated integration of multiple chemical logic switches. This provides a systemic solution to overcome the tolerance challenges in GBM immunotherapy.

Among the above stimulus-responsive nanocarriers, ICD is not universally involved; however, as a key immune-activating mechanism, it can link responsive nanocarriers-induced tumor damage with adaptive antitumor immunity. Notably, the efficiency and mechanisms of ICD induction differ substantially among different response modes. Physical triggers, such as PDT, sonodynamic therapy (SDT), photothermal therapy (PTT), and radiotherapy, mainly induce ICD through ROS generation, thermal stress, mitochondrial dysfunction, and endoplasmic reticulum stress [158]. In contrast, microenvironment-responsive strategies can promote ICD by enhancing tumor-selective cytotoxicity and DAMP release. These DAMP signals subsequently drive dendritic cell maturation and antigen cross-presentation, leading to $CD8^+$ T cell priming and the establishment of durable antitumor immune memory.

Although multi-responsive nanocarriers can improve the precision of drug release and enhance therapeutic efficacy, their complex design and fabrication processes may undermine their potential for clinical translation. Therefore, efforts should also be directed toward developing structurally simpler nanocarriers to facilitate the clinical advancement of cancer immunotherapy.

8. Summary and Outlook

The highly complex immunosuppressive network and abnormal physicochemical microenvironment within GBM tissues collectively present a formidable therapeutic barrier that severely restricts the clinical outcomes of conventional immunotherapies. Stimuli-responsive nanocarriers that target the physicochemical characteristics of tumors offer a highly promising strategy to overcome this bottleneck. These advanced platforms hold the potential to completely

dismantle the immunosuppressive barrier by intelligently responding to specific TME triggers, such as pH gradients, overexpressed enzymes, and altered redox potentials, to achieve spatiotemporally controlled drug release or in situ structural transformations, paving the way for next-generation precision immunotherapy. In particular, the evolution from single-responsive strategies to multiple logic-gated designs (such as pH/GSH dual responsiveness) enables nanocarriers to more precisely coordinate diverse therapeutic modalities, thereby profoundly expanding the boundaries of tumor immunotherapy.

Compared with systemically administered immunotherapies, the utilization of novel nanocarriers for immunotherapy holds immense potential to significantly enhance tumor selectivity and mitigate the risk of systemic toxicities. However, to fully evaluate these advantages and support clinical translation, more standardized quantitative reporting is required in preclinical studies of TME-responsive nanocarriers. Key parameters, such as tumor-to-normal tissue accumulation ratios, blood circulation half-life, clearance, are not consistently provided across different studies. In particular, the lack of matched biodistribution data in tumors and normal tissues at the same time points makes it difficult to reliably evaluate tumor selectivity and compare different nanocarriers. Therefore, future studies should adopt more standardized pharmacokinetic, biodistribution, therapeutic efficacy, and safety evaluation criteria to facilitate rigorous cross-study comparison and clinical translation.

Despite the tremendous promise of nanocarriers in cancer immunotherapy, the clinical translation of TME-responsive nanocarriers continues to face formidable challenges. First, GBM possesses high heterogeneity. The microenvironmental characteristics, such as pH values or GSH concentrations, vary significantly among different patients and even within the same tumor. This variability causes uncertainties in the therapeutic efficacy of nanocarriers that rely on specific

stimulus thresholds across different individuals. Second, it is often difficult to predict the complex in vivo biological dynamics of nanocarriers, which may result in off-target effects or nonspecific accumulation within the reticuloendothelial system, potentially triggering immune toxicity [159]. Furthermore, high manufacturing costs, regulatory hurdles, uncertainties surrounding long-term toxicity, and biocompatibility constitute major obstacles to their clinical translation. While nanocarriers are promising as cancer immunotherapeutics, further research is imperative to comprehensively understand their pharmacological profiles, immune recognition, and long-term safety, thereby enhancing their clinical applicability and impact on cancer therapy.

To maximize the clinical benefits of responsive nanocarrier-mediated GBM immunotherapy, it is imperative to develop nanocarriers with heightened sensitivity to microenvironmental stimuli and broader response thresholds, or to integrate companion diagnostics (CDx) for personalized precision therapy. Furthermore, the deep fusion of TME-targeting strategies with exogenous physical stimuli, such as near-infrared light (for photothermal/PDT) and ultrasound (for sonodynamic therapy), holds promise as the key to overcoming the bottlenecks of GBM immunotherapy. Finally, leveraging a dual physical-biochemical regulatory mechanism would enable a synergistic approach to further dismantle immune tolerance and reinvigorate the antitumor defense.

Table 1. Applications of pH-sensitive nanocarriers in GBM immunotherapy.

Type	Nanocarriers	Response Section	Immune activator	Highlights	Tumor Grow Inhibition (TGI
Bond cleavage	PCPA&PPM @TR	Ketal linkage and DAK linker	R848	**pH-responsive hierarchical targeting for drug resistance reversal and macrophage reprogramming:** (1) The micelle core exposes MAN to specifically target GBM cells and release TMZ, inducing the ICD. (2) By targeting TME TAMs and releasing R848, the micelles reprogram M2 into M1 phenotypes, driving robust DC maturation and T-cell-mediated immune responses.	NR
	FBFO@HM @aOPN	Benzoyl imine linkage	FBFO, OMVs and aOPN	**Smart Nanocarriers Responds to the TME to activate photodynamic and dual-immune synergistic therapy for GBM:** (1) In combination with photodynamic therapy, FBFO induces ICD. (2) OMVs reprogram the phenotype of macrophages, and this immune response can also produce potent synergy with anti-PD-1 therapy, leading to long-lasting immune memory.	~ 93% estimated Fig. 6h
	AE-NPs	Zn^{2+}-imidazole coordination	Zn^{2+}	**pH-responsive AE nanocarriers cross the blood-brain barrier to target GBM, induce mitochondrial pyroptosis, and activate antitumor immunity:** (1) Zn^{2+} released upon the degradation of the ZIF-8 carrier acts as a positive regulator	~ 80% estimated Fig. 6E

		bond		of both innate and adaptive immunity, synergistically promoting the maturation of DCs.	
	IL-12 mRNA@cRGD-CM-$CaCO_3$ NPs	$CaCO_3$	IL-12 and $CaCO_3$	**cRGD/CM dual-targeted $CaCO_3$ nanocarriers induce tumor cell necrosis via ultrasound and deliver IL-12 mRNA to activate anti-glioma immunity:** (1) $CaCO_3$ induces glioma cells to release TAAs and DAMPs, thereby promoting the maturation of dendritic cells DCs. (2) IL-12 stimulates the proliferation and activation of CTLs and induces the secretion of pro-inflammatory cytokines such as IFN-γ.	~ 94%-95% esti from Fig. 5
Charge reversal	NP-MnP-ADU	PC6AB	MnP and ADU-S100	**TME-responsive organic-inorganic copolymer nanostimulators activate the STING pathway to enhance immunotherapy for glioma:** (1) MnP and ADU-S100 activate the cGAS-STING immune pathway, induce M1 polarization of tumor-associated macrophages.	~ 85–90% estir from Fig. 5
	$PCNP_{CPI/TMZ}$	PHIS	CPI-444 and TMZ	**Acid-responsive nanocarriers trigger extracellular drug release to block the adenosine pathway and reverse immunosuppression in GBM:** (1) TMZ induces ICD in glioma cells, triggering the release of DAMPs such as CRT, HMGB1, and ATP. (2) CPI-444 blocks the adenosine-A2AR pathway to promote the maturation of DCs.	~ 76% estimated Fig. 4C
	PCL-PSDMA-PTX	Sulfonamide group	PTX	**Charge-reversed amphiphilic PCL−PSDMA micelles efficiently deliver chemotherapeutic drugs and inhibit GBM growth:** (1) PTX induces immunogenic effects by killing tumor cells, inhibits cell division, and significantly suppresses the growth of U87MG and U251MG.	~ 97–99% estir from Fig. 7
Conformational change	BEAGA/ApoE-PDHD	Amino group	R848 and ILD	**GGT-Activated Nanoprobe-Mediated Synergistic Sonodynamic Immunotherapy Against GBM:** (1) Under LFUS irradiation, the sonosensitizer ILD generates a large amount of ROS, triggering ICD and releasing DAMPs. (2) The released DAMPs synergize with the small-molecule immunostimulator R848 to potently activate antigen-presenting cells and promote DCs maturation.	TGI >90% estir from Fig. 7
	$AMD@iNP_{DBCO}$ $CPI@iNP_{N^3}$	Tertiary amino group	AMD3100 and CPI-444	**Acid-triggered in situ self-assembling nanocarriers targeting extracellular dual pathways to induce ICD and reverse immunosuppression:** (1) AMD3100 blocks the CXCL12/CXCR4 signaling pathway, inducing ICD in tumor cells. (2) CPI-444 inhibits A2AR, counteracts the immunosuppression caused by the conversion of ATP generated by ICD into adenosine, maintains T-cell activity, reduces the infiltration of TAMs, MDSCs, and Tregs, and promotes the polarization of M2 TAMs to M1.	~ 78% estimated Fig. 4C
	TfR/TATH7/PTX/R837 NMs	Imidazole group	R837 and PTX	**pH-sensitive TfR-targeted nanomicelles mediate chemo-immuno synergy to remodel the tumor microenvironment:** (1) R837 activates the TLR7 pathway, induces macrophage polarization, promotes the secretion of antitumor factors, lifts immune suppression, and activates T cells.	~ 60-65% at Ds estimated from F
	MMAE@FAPtp-HFn	HFn protein nanocage	MMAE	**FAP/TfR1 dual-targeted ferritin nanocarriers activate STING and inhibit PD-L1, thereby reversing T-cell exhaustion:** (1) Released MMAE induces tumor cells and triggers ICD, releasing danger signals such as HMGB1, and significantly upregulates the expression of the chemokine CXCL10, thereby activating the type I interferon signaling pathway and recruiting $CD8^+$ T lymphocytes, which highly express Granzyme B.	~ 83.5% estim from Fig. 6

*Approximate values estimated from published graphical data when exact numerical values were not provided in the original articles.

Table 2. Representative ROS-responsive and GSH-responsive nanocarriers for immunotherapy of GBM

Target	Nanocarrier	Response Section	Size and Zeta potential	Core	Highlights	T Inhil
ROS	AMNP@J+C	borate bond	168 nm	JQ1 and Ce6	**The ROS-responsive AMNP@J+C exerts its immunotherapeutic effects through a cascading synergistic interaction between SDT-induced immunization" and "small-molecule blockade of immune checkpoints":** (1)Under ultrasound stimulation, Ce6 generates ROS, which directly disrupts the mitochondrial membrane potential of tumor cells and induces ICD. (2)JQ1 significantly reduces PD-L1 expression on the surface of GBM cells by inhibiting BRD4, thereby blocking immune evasion mediated by the PD-1/PD-L1 pathway and restoring the tumor-killing activity of CTLs.	
	ALBTA	Phenylboronic acid group	≈120 nm, ≈10 mV	TMZ, siTGF-β and SPIONs	**ROS-responsive nanocarrier ALBTA for the synergistic treatment of GBM via chemotherapy and RNAi-mediated immunomodulation:** (1) Once inside the cell nucleus, TMZ acts as an alkylating agent, inducing DNA damage and apoptosis in GBM cells, during apoptosis, DAMPs are released, thereby activating an immune response. (2) Downregulation of TGF-β significantly promotes T-cell proliferation and reduces the number of Treg cells.	
	AO@PTP/47aD	Thioacetone linkage	95 nm, -20 mV	siCd47 and DOX	**ROS-responsive nanocarriers AO@PTP/47aD enhance the immunotherapy of GBM by overcoming the inherent immune resistance and adaptive immune resistance of GBM:**	~ 86

					(1) DOX induces ICD, releases DAMPs, and activates DC maturation. (2) siCd47 silences CD47, blocks the "don't eat me" signal, and enhances the phagocytosis of tumor cells by GAMs. (3) The outer layer of ΔmsbB OMVs contains immunogenic substances that act as natural adjuvants by activating the NF-κB pathway, reprogramming M2-type GAMs into M1-type cells.	
	SeM@GL NPs	Dichalcogenide bond	120 nm	di-MSA-2 and TB-Se	**ROS-responsive synergistic sonodynamic and immunomodulatory therapy:** (1) Under ultrasound stimulation, the photosensitizer TB-Se generates a large amount of ROS, which directly kills tumor cells and induces ICD. (2) ROS-induced release of MSA-2 activates the cGAS-STING pathway, promoting DC maturation and IFN-β secretion. (3) Surface CXCR4-targeting peptides not only enhance tumor targeting but also block the CXCL12/CXCR4 signaling axis, thereby reducing the infiltration of MDSCs and Tregs.	~ 94
	^{Cas9}ARLP/sgRNA	phenylboronic acid	70 nm	sgSTAT3 and Cas9	**ROS-responsive Cas9/sgRNA-loaded nanocarriers:** (1)Knocking out STAT3 downregulates VEGF expression, promotes tumor vascular normalization, opens a pathway for the massive infiltration of antitumor immune cells into the tumor, alleviates the immunosuppressive microenvironment, and triggers a robust antitumor immune response.	~ 94
GSH	FMDM@PNGs	Disulfide bond	369.8 ± 10.4 nm, −9.88 ± 0.5 mV	DOX, MnO_2, R837 and DER	**GSH-responsive therapeutic nanovaccines for the combined treatment of GBM:** (1)The chemotherapeutic effect of DOX synergizes with the CDT effect of Mn^{2+} to induce the ICD effect; the released Mn^{2+} can directly activate the cGAS-STING signaling pathway within tumor cells, promoting the secretion of IFN-β and enhancing the immune response. (2)The immunostimulant R837, encapsulated in a membrane, binds to Mn^{2+}, thereby promoting the maturation of DCs while also repolarizing M2 macrophages into M1 macrophages.	~ 88
	A2-APM	Disulfide bond	58.8 nm, +21.64 ±0.92 mV	aPD-L1 and PTX	**GSH-responsive brain-targeted chemotherapeutic-immunotherapeutic synergistic nanomicelles:** (1)The released chemotherapeutic agent PTX kills tumor cells while inducing ICD and releasing DAMPs. (2)Released aPD-L1 blocks immunosuppressive pathways, when combined with the potent antigen-presenting capacity of mature DCs, it significantly increases the infiltration of $CD8^+$ T cells into tumors, reduces the proportion of Tregs and MDSCs, and promotes the shift of macrophages toward an anti-tumor phenotype, ultimately eliciting a potent and durable anti-GBM immune memory.	>
	OMV@HM-T/F	MnO2	100 nm, -20 mV - -30 mV	OMVs, Tuni, and Fax	**GSH-responsive biomimetic nano-interferers targeting sialic acid metabolism:** (1)Tuni and Fax synergistically inhibit glycosylation and sialic acid activation, exposing tumor antigens and enhancing immune recognition. (2)By preventing inhibitory receptor interactions, reduced surface sialic acid depletes immunosuppressive cells (M2, Tregs, MDSCs) and enhances DC antigen presentation, thereby recruiting abundant CD8+ T and NK cells.	~ 70
	ANPss(Cas9/sgGDF15)	Disulfide bond	124 nm, +24.65±3.79 mV	Cas9 and sgGDF15	**GSH-responsive nanocarriers exert their effects through "gene-editing-targeted blockade combined with immune microenvironment remodeling":** (1)GDF15 deficiency leads to a reduction in M2 macrophages in the tumor microenvironment and their extensive conversion into antitumor M1 macrophages. (2)In combination with α-PD-1 antibodies, it enhances the efficacy of ICB therapy and prolongs survival.	

*Approximate values estimated from published graphical data when exact numerical values were not provided in the original articles.

Table 3. Multi-responsive nanocarriers for immunotherapy of GBM

Target	Nanocarriers	Size and Zeta potential	Core material	Anti-GBM immune response	Tur Inhibit
PH/GSH	M@TP	173.2 nm, -40.6 ± 1.1 mV	TMZ, PC-ss-Pro and U251MG-R cell membranes	**pH/GSH-responsive biomimetic PROTAC nanocapsules for degrading BRD4 in plastic tumors to enhance antitumor immunity:** (1) BRD4 degradation effectively suppresses PD-L1 expression in tumor cells and enhances T-cell infiltration and activation. (2) Reshaping the phenotypes of dendritic cells and macrophages. (3) Combined TMZ and M@P therapy increases serum levels of pro-inflammatory cytokines and decreases levels of anti-inflammatory cytokines.	> 90%

PH/GSH	GCNP	139.8 ± 14.3 nm, −20.5 ± 3.9 mV	CRISPR/Cas9	**A glycation cascade response to nanocarrier-mediated PD-L1 knockout reverses T-cell exhaustion:** (1) The CRISPR/Cas9 system targets and edits the PD-L1 gene in GBM cells, thereby reversing T-cell exhaustion mediated by the PD-1/PD-L1 pathway and restoring T-cell proliferation and cytotoxic activity. (2) increases levels of pro-inflammatory cytokines, further activating immune cells such as T cells and macrophages. (3) The proportions of Granzyme B^+ $CD8^+$ T cells, IFN-γ^+ $CD8^+$ T cells, and $Ki67^+$ $CD3^+$ T cells in GBM tissue are significantly elevated, leading to a sustained antitumor immune response.	
pH/GSH	Cu-MOF@DPCPX	35.6 nm, 19.8 mV	DPCPX and Cu-MOF	**pH/GSH dual-responsive Cu-MOF@DPCPX nanocarriers induce immunogenic cell death and promote macrophage and T-cell infiltration:** (1) DPCPX enhances immune regulation by targeting ADORA1, synergizes with Cu^{2+}-mediated cytotoxicity, promotes macrophage polarization, increases $CD8^+$ T cell infiltration in tumor tissue, suppresses $CD4^+$ T cell function, and breaks immune tolerance.	~ 67%
pH/ROS	DNG-TPZ/IFN-γ	118.4 nm, -21.6 mV	TPZ and IFN-γ	**pH/ROS-responsive dendrimeric nanogel co-delivery of TPZ/IFN-γ for activating antitumor immune therapy in glioma:** (1) TPZ induces DNA strand breaks in tumor cells, and apoptotic tumor cells release DAMPs. (2) As a key immunomodulator, IFN-γ promotes macrophage polarization and DCs maturation, enhances the infiltration and activation of $CD4^+$/$CD8^+$ T cells in the spleen and at the tumor site, suppresses the proportion of Treg cells.	> 80%
pH/ROS	RMM@GEM NPs	230.18±2.9 nm, -13.98±0.7 mV	GEM	**pH/ROS-responsive biomimetic RMM@GEM NPs activate the STING pathway and downregulate PD-L1, reversing T-cell exhaustion to combat tumors:** (1) The released GEMs can induce double-strand breaks in tumor cell DNA, activate the intracellular cGAS-STING immune signaling pathway, trigger the ICD effect, and enhance the cross-presentation capacity of dendritic cells. (2) β-CD reverses immune evasion: β-CD specifically depletes cholesterol from the tumor cell membrane, disrupting the stable binding of PD-L1 to cholesterol, inhibiting PD-L1 upregulation triggered by STING pathway activation, blocking PD-1/PD-L1-mediated immune evasion, and reversing $CD8^+$ T-cell exhaustion.	~ 96.. fro
GSH/MMP	^{MA}PDCs	95 nm	CPT and R848	**Dual-responsive peptide-conjugated nanocarriers reprogram macrophage polarization to enhance the efficacy of chemotherapy:** (1) After ^{MA}PDCs are phagocytosed by GAMs, they release R848 under the influence of GSH, and induces the polarization of M2 macrophages into M1 macrophages.	~ 98.0 fro
pH/MMP	Dual-NP	168.77±3.45nm, 13.73±0.98mV	Dox	**A cross-linked nanocarriers with dual MMP and pH responsiveness promotes prolonged drug retention and deep penetration:** (1) Dox induces apoptosis in GBM cells by inhibiting DNA topoisomerase II. This apoptotic process triggers the release of DAMPs, including the surface exposure of CRT and the secretion of HMGB1, which subsequently promotes DCs maturation and initiates an adaptive immune response.	

*Approximate values estimated from published graphical data when exact numerical values were not provided in the original articles.

Abbreviations:

Glioblastoma (GBM)

Blood-brain barrier (BBB)

Blood-brain tumor barrier (BBTB)

Tumor microenvironment (TME)

Temozolomide (TMZ)

Immune checkpoint blockade (ICB)

Glutathione (GSH)

Reactive oxygen species (ROS)

Tumor-associated macrophages (TAMs)

Hypoxia-inducible factor-1α (HIF1α)

Cytotoxic T cells (CTLs)

Glioma stem cells (GSCs)

Transforming growth factor β2 (TGFβ2)

Hypoxia response elements (HREs)

Myeloid-derived suppressor cells (MDSCs)

Natural killer (NK)

Colony-stimulating factor 1 (CSF-1)

Monocyte chemoattractant protein-1 (MCP-1)

Matrix metalloproteinase (MMP)

Nanoparticles (NPs)

Photodynamic therapy (PDT)

Sonodynamic therapy (SDT)

Photothermal therapy (PTT)

Doxorubicin (DOX)

Danger-associated molecular patterns (DAMPs)

Dendritic macromolecular nanogels (DNGs)

Extracellular matrix (ECM)

Immunogenic cell death (ICD)

Dendritic cells (DCs)

Paclitaxel (PTX)

Declarations

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Author contributions

Cuicui Wang and Zhihong Sun was primarily responsible for writing the original draft and contributed to manuscript review and editing. Jun Sun and Jie Liu contributed to the original draft preparation and created all visualizations. Qi Zhao contributed to the conceptualization, review, and editing of the manuscript. Chengming Sun and Yong Sun supervised the entire project, secured funding, and led the conceptualization, review, and final editing of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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