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REVIEW

A Systematic Review of Nanoparticle-Mediated Ferroptosis in Glioma Therapy

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Abstract: Glioma, a highly malignant central nervous system tumor, exhibits aggressive invasiveness, extensive infiltration, and poor prognosis. Conventional treatments such as surgery, radiotherapy, and chemotherapy are hindered by limitations including the inability to overcome the blood-brain barrier (BBB), drug resistance, and high recurrence rates. Ferroptosis induced by nanoparticle-based systems offers an innovative strategy for glioma therapy by efficiently traversing the BBB, precisely delivering ferroptosis inducers, enhancing tumor accumulation, and enabling stimuli-responsive drug release. These features collectively improve the induction efficiency of ferroptosis in glioma cells. Various nanoplatforms, including inorganic nanoparticles, biomimetic carriers, and polymer-based systems, have demonstrated potential in crossing the BBB, inducing ferroptosis, and suppressing glioma progression. These systems enhance reactive oxygen species generation, deplete glutathione, and disrupt tumor microenvironment defense mechanisms, achieving synergistic therapeutic effects. The integration of ferroptosis with nanotechnology is emerging as a promising, non-invasive strategy for the treatment of gliomas, offering substantial therapeutic potential.

Keywords: ferroptosis, glioma, nanoplatforms, synergy

Introduction

Glioma is a malignant neoplasm of the central nervous system, characterized by its aggressive invasiveness, extensive infiltration, and high postoperative recurrence rates.[1–3] Standard therapeutic approaches, including surgery, radiotherapy, and chemotherapy, yield a median survival time of approximately 20 months, with 2-year and 5-year survival rates of 27% and 10%, respectively.[4,5] Despite these interventions, the high rate of postoperative recurrence and the inability of conventional chemotherapy agents to effectively cross the blood-brain barrier (BBB) and blood-brain tumor barrier (BBTB) significantly limit their therapeutic efficacy.[6,7] Additionally, the development of drug resistance further complicates the complete eradication of glioma.[8]

In 2012, the concept of ferroptosis was introduced, defining it as a unique form of cell death that differs from traditional modes, characterized by iron accumulation and lipid peroxidation.[9,10] Unlike apoptosis, ferroptosis is not associated with chromatin condensation, the membrane rupture typical of necrosis, or the formation of double-membrane autophagosomes.[11] Morphologically, ferroptosis is characterized by mitochondrial shrinkage, increased membrane density, and the loss or reduction of mitochondrial cristae;[12] Biochemically, ferroptosis involves the oxidation of lipids by Fe^{2+} through the Fenton reaction, leading to the accumulation of reactive oxygen species (ROS), depletion of glutathione, and inhibition of glutathione peroxidase 4 (GPX4), preventing the reduction of lipid peroxides and ultimately triggering ferroptosis.[13] Given that cancer cells, including those in brain tumors, require elevated levels of iron, many tumors exhibit heightened sensitivity to ferroptosis.[14,15] As such, ferroptosis represents a promising novel strategy to improve the treatment and prognosis of glioma and related malignancies.[16]

Revisions:Nanomaterials have garnered considerable attention for their ability to address the limitations of conventional ferroptosis-inducing approaches, such as targeted delivery, stable drug loading, and intelligent controlled release.[17] Due to their exceptional physical and chemical properties, nanomaterials can be precisely engineered to control various

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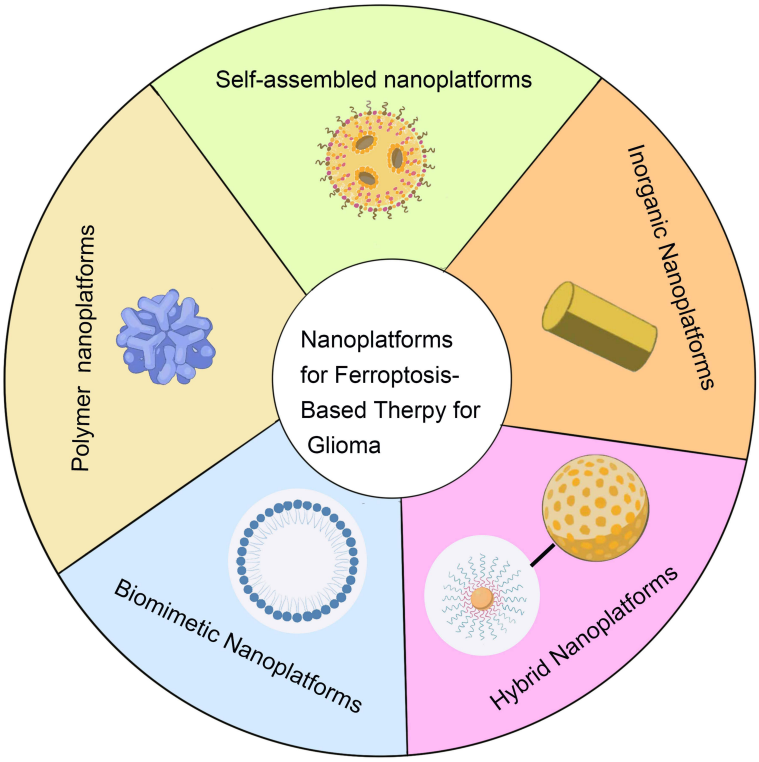

Figure 1 Common Nanocarriers Employed in Ferroptosis-Based Glioma Therapy.

characteristics and functionalized to achieve optimal therapeutic effects.[18] Nanomaterials are typically defined as substances with at least one dimension less than 100 nm.[19] A variety of nanomaterials are currently being investigated for their potential in glioma therapy.[20] Through ligand modification, nanomaterials can effectively cross the BBB and BBTB, allowing for targeted delivery to glioma cells.[21,22] The advantages of nanomaterials in glioma treatment include: (1) enhanced drug stability, (2) favorable biocompatibility, (3) the ability to deliver multiple therapeutic agents for synergistic effects, and (4) their small size and modifiability, which facilitate easier passage across the BBB and BBTB.[23,24] Consequently, nanoparticle-based therapies show significant promise in advancing glioma treatment.[25] Self-assembly platforms spontaneously form ordered structures through a variety of intermolecular non-covalent interactions, including hydrogen bonding, van der Waals forces, electrostatic interactions, and hydrophobic effects.[26,27] Revisions: Polymeric nanocarriers—such as micelles, nanogels, vesicles, and dendrimers—are considered promising candidates for chemotherapy drug delivery systems (DDS) due to their excellent biocompatibility and biodegradability.[28] Organic nanocarriers are composed of organic materials or compounds, forming stable nanoparticle systems, while hybrid nanoplatforms integrate inorganic nanoparticles within organic matrices to achieve multifunctional synergistic effects.[29] Moreover, the incorporation of cell membrane technologies endows these nanocarriers with biological activity, further enhancing their therapeutic potential.[30] Figure 1 illustrates the types of nanocarriers employed in ferritin-based glioma therapy.

Overview of Ferroptosis

Basic Concepts and Characteristics

Ferroptosis is an iron-dependent, programmed form of cell death that occurs when the cellular balance between lipid peroxidation and repair is disrupted, resulting in the excessive accumulation of lipid-derived reactive oxygen species (ROS) and, ultimately, cell death.[31] Ferroptosis is fundamentally distinct from traditional forms of cell death, such as apoptosis, autophagy, and necrosis, in terms of its biochemical, morphological, and genetic mechanisms.[32] Morphologically, ferroptosis is characterized by notable alterations in the mitochondria, including mitochondrial

shrinkage, loss of mitochondrial cristae, and an increase in mitochondrial membrane density. Biochemically, lipid peroxidation represents the central hallmark of ferroptosis, where ROS oxidize polyunsaturated fatty acids (PUFAs), generating lipid hydroperoxides. This process is catalyzed by iron accumulation, which facilitates the Fenton reaction, leading to the generation of additional ROS. Genetically, ferroptosis is primarily regulated by genes involved in iron homeostasis and lipid peroxidation metabolism.[33–36]

Mechanisms of Ferroptosis

Revisions:Ferroptosis is a form of programmed cell death that is iron-dependent and driven by lipid peroxidation. Its occurrence involves multiple processes, including dysregulated iron metabolism, accumulation of reactive oxygen species (ROS), and impaired antioxidant defense systems. Iron plays a pivotal role in initiating this process. Under physiological conditions, iron homeostasis is tightly regulated through mechanisms such as storage (ferritin), uptake (cystine/glutamate antiporter system Xc^- and transferrin [TF]), utilization (hemoglobin and Fe–S clusters), and export (ferroportin, SLC40A1).[37,38] When iron metabolism becomes unbalanced, excess free Fe^{2+} can catalyze the Fenton reaction, generating large amounts of ROS. This triggers lipid peroxidation and disrupts cell membrane integrity, ultimately leading to cell death.[39]

Another hallmark of ferroptosis is the inactivation of the cellular antioxidant defense system, particularly the Xc^-–glutathione (GSH)–glutathione peroxidase 4 (GPX4) axis. Mechanistically, this axis serves as a central regulatory pathway of ferroptosis. The Xc^- system contributes to GSH synthesis, sustaining the cell's antioxidant capacity. GSH, in conjunction with GPX4, scavenges lipid peroxides and suppresses the onset of ferroptosis.[40] The tumor suppressor p53 can inhibit cystine uptake by repressing the Xc^- system and downregulating SLC7A11 expression, thereby reducing GPX4 activity. This leads to diminished antioxidant capacity, elevated ROS levels, and induction of ferroptosis.[41] Inhibition or inactivation of GPX4 is a critical event in the regulation of ferroptosis.[42] GPX4 catalyzes the conversion of GSH to oxidized glutathione (GSSG) and detoxifies lipid hydroperoxides (L-OOH) into less toxic lipid alcohols (L-OH), thereby mitigating peroxidative stress.[43]

Chen et al[44] reported that Mauritania disrupts this pathway by downregulating GPX4 and SLC7A11 expression. The mevalonate (MVA) pathway[45] further contributes to ferroptosis by influencing GPX4 biosynthesis through the regulation of selenocysteine tRNA maturation, thereby enhancing lipid peroxidation. Accumulation of phospholipid hydroperoxides (PLOOHs) that are not neutralized by GPX4 triggers radical chain reactions, leading to membrane damage.[46,47] Moreover, the ALOX enzyme family[48] directly catalyzes the oxidation of polyunsaturated fatty acids (PUFAs), accelerating the process. In addition, ferroptosis suppressor protein 1 (FSP1) functions via the NADPH/CoQ10 axis to regenerate antioxidants; decreased FSP1 activity further compromises the cell's resistance to lipid peroxidation.[49] The interplay among these pathways (Figure 2) leads to a surge in ROS, collapse of the antioxidant defense system, and loss of membrane integrity, ultimately resulting in ferroptotic cell death.

Blood-Brain Barrier and Blood-Brain Tumor Barrier

The physiological barriers of the brain constitute the primary impediments to drug penetration into the central nervous system. A comprehensive understanding of these various barriers (Figure 3) is essential for the development of effective strategies aimed at targeting the brain.

Blood-Brain Barrier

Revisions: The blood–brain barrier (BBB) is primarily composed of brain capillary endothelial cells (BCECs), pericytes, and astrocytes. Astrocytes, the most abundant type of glial cell in the central nervous system (CNS), exhibit complex morphologies and heterogeneous distributions. Their terminal end-feet are capable of contacting the vascular basement membrane and are extensively involved in various physiological functions, including modulation of neural signaling, clearance of metabolic waste, and regulation of cerebral blood flow.[50–52] Pericytes are closely apposed to the endothelial cells of capillaries, and their intimate interactions are essential for maintaining the structural and functional stability of the BBB. While the BBB plays a crucial role in protecting the brain from toxins and pathogens, it also poses a significant barrier to drug delivery, thereby limiting therapeutic efficacy for brain disorders such as neurodegenerative diseases and brain tumors.[53]

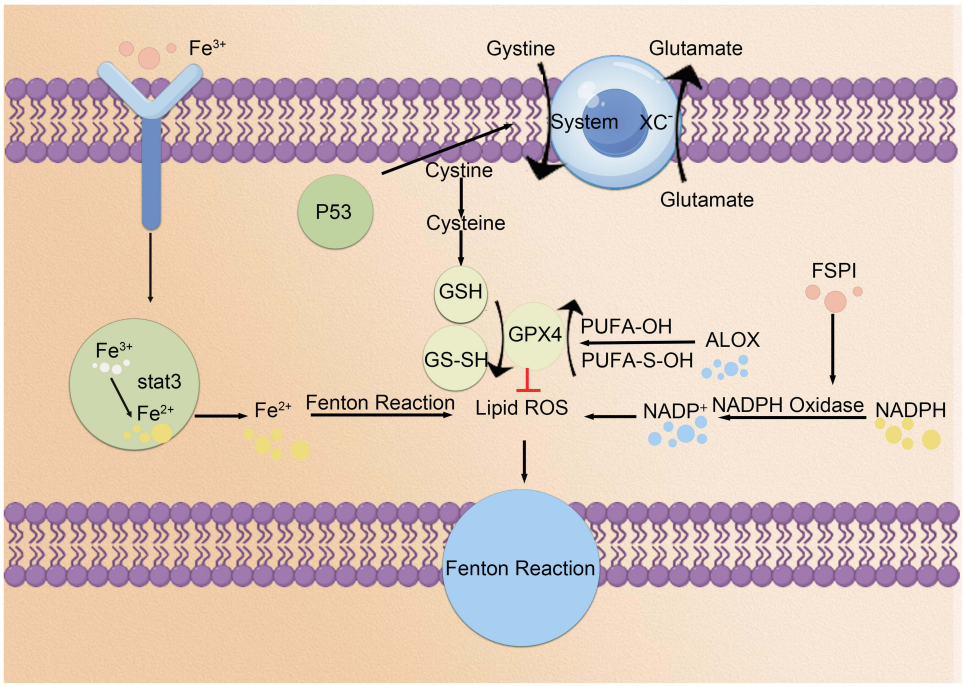

Figure 2 Molecular Mechanisms Underlying Ferroptosis.

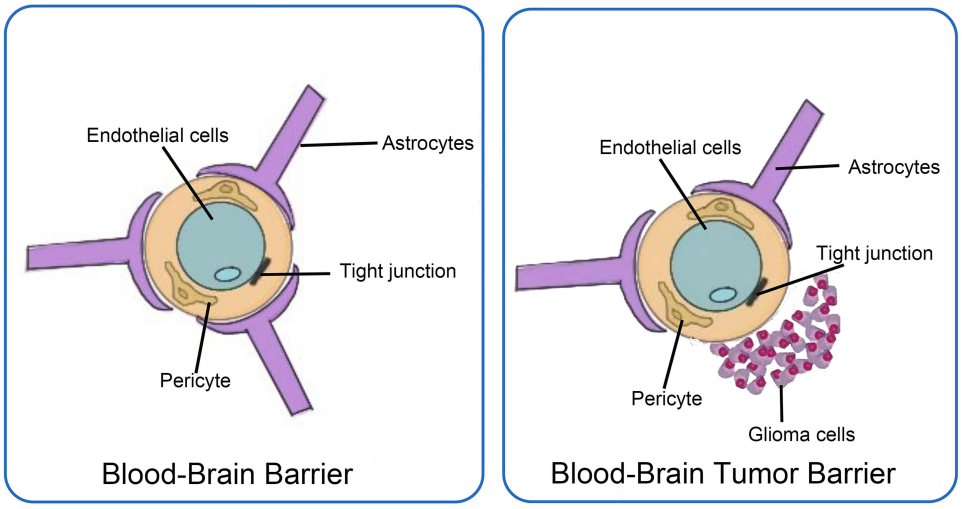

Figure 3 Schematic Representation of the Blood–Brain Barrier and Blood–Brain Tumor Barrier.

BCECs form the core structural component of the BBB, lining the inner wall of brain microvessels. Through highly coordinated interactions with other CNS-resident cells, BCECs maintain the barrier's selective permeability. Compared with peripheral endothelial cells, BCECs possess tighter tight junctions and adherens junctions, which effectively prevent paracellular diffusion of molecules, significantly restricting the entry of most anticancer agents into brain tissue. The transendothelial electrical resistance (TEER) of BCECs can reach as high as 1500–2000 Ω·cm², reducing paracellular permeability to macromolecules and hydrophilic compounds by approximately 50–100 fold.[54,55] In addition, these endothelial cells exhibit a high mitochondrial density and express a wide array of metabolic enzymes, including peptidases, nucleotidases, esterases, phosphatases, and cytochrome P450 enzymes, endowing them with substantial metabolic degradation capacity to efficiently clear exogenous compounds.[56,57]

Within the biochemical barrier of the BBB, transport proteins—particularly ATP-binding cassette (ABC) transporters—are highly expressed in BCECs and function as active drug efflux pumps. These transporters can expel a broad range of chemotherapeutic agents from brain tissue, severely limiting the accumulation of small-molecule targeted drugs in the CNS.[58] Despite significant progress in targeted therapies for non-CNS solid tumors over the past decade, the restrictive nature of the BBB remains a major obstacle to the successful development and application of novel therapeutic strategies for glioblastoma (GBM).

Blood-Brain Tumor Barrier

Revisions:The blood–brain tumor barrier (BBTB), formed by capillaries within brain tumors, exhibits distinct characteristics compared to the blood–BBB. A series of pathological alterations induced by malignant tumor cells disrupts the structure and function of the BBB, resulting in unique drug delivery pathways across this barrier and significantly influencing drug distribution and delivery patterns within the central nervous system (CNS). In glioblastoma (GBM), abnormal angiogenesis and increased vascular permeability are common, giving rise to a functionally discontinuous BBTB between tumor-associated capillaries and surrounding brain tissue.[59]

However, despite the relatively enhanced permeability of the BBTB, it remains a substantial obstacle for drug delivery. On one hand, tight junction proteins—such as zonula occludens (ZO) proteins—are partially retained between tumor-associated endothelial cells. This retention restricts the paracellular transport of polar drugs into tumor tissue, especially at the interface between the tumor margin and the intact BBB, where drug penetration is further limited.[60] This barrier effect significantly hampers the ability of anticancer agents to enter the CNS and effectively target GBM tissues. Therefore, achieving efficient penetration of the BBTB and optimizing drug delivery strategies remain critical challenges in GBM therapy. In addition, the BBTB exhibits high expression levels of multiple efflux transporters, including P-glycoprotein (P-gp), multidrug resistance-associated proteins (MRP1, MRP3), and breast cancer resistance protein (BCRP). These active efflux systems further limit the accumulation of various chemotherapeutic agents within tumor regions and represent a major mechanism underlying therapeutic resistance in GBM.[61,62]

The presence of the BBTB significantly impedes the efficient delivery of therapeutic agents to the tumor. The combined effect of the BBB and the BBTB constitutes the principal barrier to drug delivery in the context of brain tumors. Despite the disruption of the BBTB, regions of the BBB persist throughout the entire GBM barrier system, preventing substantial drug accumulation at all tumor sites. This phenomenon is a major reason for the limited efficacy of most chemotherapeutic agents in GBM treatment, as well as for the inevitable recurrence of the tumor, even following complete resection of the contrast-enhancing regions.[57] The dual presence of the BBB and BBTB obstructs the effective delivery of various chemotherapy agents to the tumor, particularly in the tumor-infiltrating areas, thereby posing a significant challenge to the successful treatment of GBM. Consequently, the development of advanced drug delivery systems capable of dual-targeting both the BBB and BBTB is of paramount importance for improving therapeutic outcomes.

Nanoparticle-Mediated Ferroptosis in Glioma Therapy

Ferroptosis, a regulated form of cell death, and its association with gliomas have garnered increasing attention in recent years. Ferroptosis plays a pivotal role in the regulation of glioma cell proliferation. Notably, the expression of ASCL4, a key marker associated with ferroptosis, is significantly reduced in glioma tissues compared to normal human brain tissue.[63] Furthermore, various ferroptosis-inducing agents, including dihydroartemisinin and amentoflavone, have demonstrated effectiveness in inhibiting glioma cell proliferation.[64,65]

Revisions: To improve the therapeutic outcomes of glioma treatment, a range of strategies have been employed to enhance the permeability of the Blood-Brain Barrier (BBB). These approaches include biochemical interventions such as drug administration, physical methods such as electromagnetic pulse therapy, and leveraging the pathological alterations induced by gliomas themselves to disrupt the BBB.[66–69] In the context of ferroptosis, nanotherapy has emerged as a promising, non-invasive treatment modality.[70] Nanodrugs designed to exploit the ferroptosis mechanism offer significant advantages, including cost-effectiveness and exceptional biocompatibility. This section provides an in-depth

discussion on nanodrugs developed based on the principles of ferroptosis, with further details presented in Table 1. We have summarized the small molecule drugs targeting ferroptosis signaling and their clinical status in Table 2.

Revisions: This section provides an in-depth discussion of nanoformulations developed based on ferroptosis principles, systematically comparing five nano-delivery platforms: inorganic nanoplatforms, biomimetic nanoparticles, polymeric carriers, hybrid nanosystems, and self-assembled systems. Each platform demonstrates unique delivery advantages

Table 1 Nanocarriers for Treating Glioma Therapy

Category	Nanoformulations	Model Drug	Advantages	Ref
Inorganic Nanoplatform	FeGd-HN@Pt@LF/RGD2	CDDP	BBB penetration (small size + LF receptor-mediated transcytosis); integrin αvβ3-mediated endocytosis; Fe^{2+}/Fe^{3+} + CDDP release (accelerates Fenton reaction → ROS generation); intrinsic MRI for ferroptosis therapy monitoring.	[71]
	IONP@PTX	PTX	Ultrafine structure + high dispersion + negative zeta potential (low aggregation); high drug loading/sustained release; validated for in vitro/in vivo use.	[72]
	MGA-CDs	–	High BBB permeability; mitochondria targeting in tumors; PLPP4 suppression → glycerophospholipid metabolism disruption (ferroptosis induction)	[73]
Biomimetic Nanoparticles	Fe3O4-siPD-L1@M-BV2	–	Orthotopic drug-resistant GBM targeting; enhanced ferroptosis + immunotherapy synergy; prolonged murine survival.	[74]
	DOX-FN/C6M-NVs	DOX	C6M-mediated homologous targeting (↑DOX accumulation in C6 glioma); ferroptosis/apoptosis induction; BBB-penetrating delivery + reduced cardiotoxicity	[75]
Polymer Nanoparticles	L-STNPs	TMZ / SRF	LAT1 targeting (↑cellular uptake/cytotoxicity/tumor accumulation/BBB penetration); enhanced glioma therapy	[76]
	S-biAb/dEGCG@NPs	–	Improved GBM targeting/penetration; immune cell infiltration activation; ferroptosis + immune checkpoint blockade synergy.	[77]
Hybrid Nanoparticles	T+E@LPs-cRGD+GelMA	TEM/ERA	αvβ3 integrin targeting (cRGD-modified); sustained TMZ/Erastin release; ↑TMZ sensitivity + ferroptosis induction; tumor immune microenvironment modulation (suppresses GBM relapse).	[78]
	hNRVs	RSL3	NK exosome tumor-homing + liposomal drug loading; selective glioma delivery (ferroptosis inducers/immune activators); no off-target organ toxicity	[79]
Self-Assembled Nanoparticles	Ce6@Cu NPs	Ce6	Enhanced BBB penetration and tumor targeting observed. Enhanced sonodynamic effects; GSH depletion → cuproptosis/ferroptosis; improved BBB penetration + tumor targeting	[80]
	FIN56-loaded graphdiyne nanoplatforms	FIN56	Photothermal-ferroptosis combo therapy; GPX4-mediated ferroptosis induction; enhanced BBB penetration + tumor targeting	[81]

Abbreviations: CDDP, Cisplatin; PTX, Paclitaxel; DOX, doxorubicin hydrochloride; SRF, Sorafenib; Ce6, chlorin e6; TMZ, temozolomide; ERA, Erastin; RSL3, Rehabilitation Support League 3.

Table 2 Small-Molecule Drugs Targeting Ferroptosis Pathways and Their Clinical Status

Drug Name	Target	Mechanism of Action	Clinical Status	Ref
Dihydroartemisinin (DHA)	GPX4	Inhibits GPX4 activity, leading to lipid peroxide accumulation	Preclinical studies	[82,83]
Erastin	System Xc^-	Blocks cystine/glutamate antiporter, reduces glutathione (GSH) synthesis, induces oxidative stress	Preclinical studies	[78]
Sorafenib (SRF)	System Xc^-	Inhibits System Xc^- activity, increases ROS generation, synergizes with anti-angiogenic effects	FDA-approved (other cancers), under investigation for glioma therapy	[76,84]
RSL3	GPX4	Directly binds and inactivates GPX4, blocking lipid peroxide detoxification	Preclinical studies	[79]
Amentoflavone	Autophagy pathway	Activates autophagy-dependent ferroptosis pathways to induce glioma cell death	Preclinical studies	[85]

Abbreviations: GPX4, Glutathione Peroxidase 4; System Xc^-, Cystine/Glutamate Antiporter; ROS, Reactive Oxygen Species; DHA, Dihydroartemisinin; SRF, Sorafenib; CDDP, Cisplatin.

and mechanistic innovations in glioma therapy, with a detailed comparative analysis of their functional characteristics and therapeutic outcomes presented in Table 1.

Revisions:Next, we will introduce the nanoplatforms individually and summarize their advantages and disadvantages in Table 3.

Table 3 Comparison of Different Nanoparticle Platforms

Category	Advantages	Limitations	Potential Applications	Ref
Inorganic Nanoparticles	1. Excellent biocompatibility and stability 2. High drug-loading capacity and controllable release 3. Easy surface functionalization (eg, ligand modification) 4. Combined diagnostic and therapeutic functions (eg, MRI imaging)	1. Long-term toxicity risks with some metal nanoparticles 2. Degradation byproducts may affect the microenvironment 3. Challenges in large-scale production	1. Blood-brain barrier penetration (eg, FeGd-HN@Pt@LF/RGD2) 2. Ferroptosis induction (eg, IONP@PTX) 3. Multimodal therapy (photothermal/ chemodynamic synergy)	[71,73,86]
Biomimetic Nanoparticles	1. Natural membrane structure enables immune evasion capabilities 2. High tumor targeting and penetration 3. Low immunogenicity and toxicity 4. Compatibility with immunotherapy (eg, PD-L1 inhibition)	1. Complex membrane extraction and coating processes 2. Low drug-loading efficiency 3. Batch-to-batch variability	1. Drug-resistant glioma therapy (eg, Fe_3O_4-siPD-L1@M-BV2) 2. Immune microenvironment modulation 3. Multi-mechanism synergy (ferroptosis + immune activation)	[87,88]
Polymeric Nanoparticles	1. Material diversity (natural/synthetic polymers) 2. High drug-loading capacity and sustained release 3. Easy surface modification (eg, PEGylation for prolonged circulation) 4. Good biodegradability	1. Potential inflammatory responses with some polymers 2. Requires additional modifications for targeting 3. Limited stability in complex microenvironments	1. Targeted delivery (eg, LAT1-targeted systems) 2. Combination immunotherapy (eg, S-biAb/dEGCG@NPs) 3. Co-delivery of multiple drugs (eg, TMZ + SRF)	[76,77,89]

(*Continued*)

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Table 3 (Continued).

Category	Advantages	Limitations	Potential Applications	Ref
Hybrid Nanoparticles	1. Multi-material synergy enhances functionality (eg, lipid-polymer hybrids) 2. Stimuli-responsive drug release (pH/ enzyme-triggered) 3. Theranostic capabilities (eg, 3D-printed hydrogel-liposomes)	1. Complex fabrication processes and high costs 2. Potential interactions between components 3. Limited long-term safety data	1. Post-surgical recurrence prevention (eg, T+E@LPs-cRGD+GelMA) 2. Immune-ferroptosis synergy (eg, hNRVs) 3. Precision drug release systems	[78,79,90]
Self-Assembled Nanoparticles	1. Simple preparation (non-covalent self-assembly) 2. High drug-loading efficiency 3. Environment-responsive release (eg, ultrasound/light activation) 4. Low toxicity with natural components	1. Poor structural stability 2. Requires modifications for targeting 3. Unclear in vivo metabolic mechanisms	1. Multi-mode cell death induction (eg, Cu@Ce6-triggered cuproptosis + ferroptosis) 2. Photothermal-ferroptosis synergy (eg, FIN56@GDY) 3. Non-traditional drug delivery (eg, DHA/ICG)	[81,91,92]

Abbreviations: MRI, Magnetic Resonance Imaging; PEG, Polyethylene Glycol; TMZ, TemozolomideSRF: Sorafenib; DHA, Dihydroartemisinin; GPX4, Glutathione Peroxidase 4; LAT1, L-Type Amino Acid Transporter 1.

Inorganic Nanoplatform

Inorganic nanoplatforms primarily consist of metal and non-carbon-based materials, such as gold nanoparticles, mesoporous silica nanoparticles (MSNs), quantum dots, upconversion nanoparticles, two-dimensional nanomaterials, and superparamagnetic iron oxide nanoparticles (SPIONs). These nanostructures are highly favored by researchers due to their exceptional biocompatibility, ability to enhance drug stability, and ease of surface modification. Moreover, their versatile tunability and potential for diagnostic applications further enhance their appeal in various biomedical fields, including glioma treatment.[21,93–95]

In the context of ferroptosis-based therapy for in situ brain tumors, Shen et al proposed a novel ferroptosis treatment strategy that is accelerated by an iron reaction, utilizing magnetic nanoparticles (FeGd-HN@Pt@LF/RGD2). This approach incorporates Fe_3O_4/Gd_2O_3 mixed nanoparticles loaded with cisplatin (CDDP) and is augmented by the addition of lactoferrin (LF) and an RGD peptide dimer (RGD_2). These nanoparticles, with a small size of 6.6 nm and the ability to cross the blood-brain barrier (BBB) via LF receptor-mediated endocytosis, are efficiently internalized by tumor cells through integrin αvβ3-mediated endocytosis. Upon endosomal uptake and subsequent degradation, Fe^{2+}, Fe^{3+}, and CDDP are released. Fe^{2+} and Fe^{3+} actively participate in the iron-driven reaction, while CDDP generates H_2O_2, which further accelerates the iron reaction. This enhanced iron reaction induces the generation of reactive oxygen species (ROS), thereby triggering cancer cell death. The FeGd-HN@Pt@LF/RGD2 nanoparticles effectively deliver the requisite reactants for the iron reaction to the tumor site, resulting in a significant inhibition of tumor growth. Furthermore, the inherent MRI capability of these nanoparticles allows for the non-invasive monitoring and assessment of the therapeutic efficacy of ferroptosis-based treatment.[71]

Similarly, Nie et al developed iron oxide nanoparticles encapsulating paclitaxel (IONP@PTX) for glioma therapy. Their studies demonstrated that IONP@PTX significantly inhibits the proliferation of U251 glioma cells by elevating iron ion concentrations, increasing ROS levels, and promoting lipid peroxidation. Additionally, it enhances the expression of autophagy-related proteins, such as Beclin1 and LC3II, while suppressing the expression of p62 and the ferroptosis-associated protein GPX4. These events ultimately lead to the inhibition of glioma cell growth via an autophagy-dependent ferroptosis pathway. In vivo studies using a glioma xenograft mouse model revealed that IONP@PTX exhibited substantial anti-tumor effects with no significant systemic toxicity, suggesting its potential as a ferroptosis inducer in tumor therapy.[72]

Zhang et al further advanced the development of an iron oxide nanoparticle-based system (IONPs) for gene therapy in glioblastoma (GBM). This system combines IONPs with cisplatin (Pt) and siRNA targeting glutathione peroxidase 4 (si-GPX4),

resulting in the formulation of FA/Pt-si-GPX4@IONPs. These nanoparticles demonstrated remarkable anti-tumor effects in U87MG and P3#GBM cell lines. Within the cells, IONPs increase iron ion concentrations, while Pt exerts its cytotoxic effects by disrupting DNA, thereby inducing apoptosis. Simultaneously, IONPs generate ROS through the Fenton reaction to promote ferroptosis and enhance therapeutic efficacy by inhibiting GPX4 expression. This nanoparticle-based formulation exhibited superior therapeutic effects and minimal systemic toxicity both in vitro and in vivo, highlighting its potential as a safe and effective therapeutic agent for GBM.[96]

Wen et al also developed IONPs loaded with paclitaxel (IONPs@PTX) to target glioblastoma (GBM) via an autophagy-dependent ferroptosis mechanism. IONPs@PTX demonstrated excellent water solubility and targeted delivery through surface modification, facilitating effective penetration of the blood-brain barrier and accumulation in tumor tissues. Furthermore, IONPs@PTX induced ferroptosis in GBM cells by upregulating ferroptosis markers and down-regulating anti-ferroptosis genes. Studies indicated that autophagy inhibition via the use of 3-methyladenine (3-MA) or shRNA-mediated silencing of autophagy-related genes such as Beclin1/ATG5 significantly reversed IONPs@PTX-induced ferroptosis, while overexpression of Beclin1/ATG5 further promoted this process. Therefore, IONPs@PTX regulates ferroptosis through a Beclin1/ATG5-dependent autophagy pathway, illustrating its potential in the treatment of GBM.[97]

Zhang et al developed a cRGD/Pt+DOX@GFNPs (RPDGs) nanoformulation designed for multi-target combination therapy and magnetic resonance imaging (MRI) tracking in the treatment of glioblastoma (GBM). The RPDGs effectively disrupt redox homeostasis in GBM cells, promoting both apoptosis and ferroptosis. By utilizing the stable Fenton reaction catalytic activity of GA/Fe^{2+} nanoparticles under physiological conditions, this formulation induces a significant increase in reactive oxygen species (ROS) levels. Additionally, Pt(IV)-mediated glutathione (GSH) depletion and enhanced ROS generation, combined with the high photothermal conversion efficiency of GA/Fe^{2+} nanoparticles, facilitate the induction of ferroptosis. Moreover, RPDGs exhibit excellent photothermal responsiveness and MRI capability, thus allowing for precise monitoring of therapeutic progress. These results suggest that RPDGs not only directly inhibit tumor growth but also enhance the delivery efficiency of conventional chemotherapy agents across the blood-brain barrier (BBB), offering a novel approach for comprehensive GBM treatment.[98]

Cao et al developed an intelligent nanoplatform, PCN-224@Au/CeO_2-Lf, for iron-independent ferroptosis therapy in situ for glioblastoma (GBM). This platform effectively penetrates the blood-brain barrier and exerts therapeutic effects through a multi-pathway mechanism. PCN-224 nanoparticles (NPs), which serve as sonosensitizers for sonodynamic therapy (SDT), are surface-functionalized with small gold nanoparticles (Au NPs) and cerium oxide (CeO_2) nanoparticles. These nanoparticles mimic the enzymatic activities of glucose oxidase (GOx), peroxidase (POD), and catalase (CAT), enabling self-supplied H_2O_2, the generation of a more acidic tumor microenvironment, and the production of cytotoxic hydroxyl radicals (·OH) and oxygen (O_2), which significantly enhance SDT efficacy. Additionally, Ce^{4+}-mediated GSH depletion further exacerbates ferroptosis and apoptosis. The combined effects of ROS generation and GSH depletion lead to the accumulation of lipid peroxides (LPO), thereby triggering iron-independent ferroptosis and effectively shrinking in situ GBM. This study is the first to demonstrate the potential of an iron-independent ferroptosis strategy in the treatment of GBM.[99]

Deng et al synthesized novel functional carbon dots (MGA-CDs) for the inhibition of glioma growth. MGA-CDs, prepared via a hydrothermal method using metformin and gallic acid precursors, exhibit excellent BBB permeability and potent anti-tumor activity. MGA-CDs specifically target the mitochondria of tumor cells, causing mitochondrial shrinkage and a reduction in cristae density. Transcriptomic analysis revealed that MGA-CDs interfere with glycerophospholipid metabolic pathways by inhibiting the expression of PLPP4, thereby inducing ferroptosis. Further in vivo studies using human-derived glioma xenograft mouse models confirmed the effective therapeutic potential of MGA-CDs, significantly inhibiting intracranial tumor growth and prolonging survival in tumor-bearing mice. This study provides a promising strategy for the development of carbon dot-based therapeutics for glioma treatment.[73]

Li et al introduced an innovative engineered exosome-magnetic nanoparticle platform (EMNPs) for the treatment of glioblastoma (GBM). This platform achieves efficient BBB penetration and targeted delivery to GBM cells through Angiopep-2-modified exosomes, while Fe_3O_4 nanoparticles enable magnetic targeting and controlled drug delivery. EMNPs enhance ferroptosis by modulating multiple pathways, including the inhibition of glutathione peroxidase 4

(GPX4) and dihydrolipoamide dehydrogenase (DHODH), thereby increasing lipid peroxidation and inducing cell death. Moreover, Fe_3O_4 nanoparticles release Fe^{2+} intracellularly, further amplifying ferroptosis. In vitro and in vivo studies demonstrated that EMNPs significantly improve therapeutic efficacy in GBM without causing appreciable organ toxicity or inflammation, suggesting their potential as a safe and effective therapeutic agent for GBM treatment.[100]

Li et al also developed a novel engineered exosome-ultrathin iron oxide framework (Exosome-UIOFs) for glioblastoma (GBM) therapy. Exosome-UIOFs, which incorporate Angiopep-2-modified exosomes, exhibit high BBB permeability and potent anti-tumor activity. These nanoparticles specifically target tumor cell mitochondria, leading to mitochondrial dysfunction and damage. Transcriptomic analysis revealed that Exosome-UIOFs inhibit the ferroptosis defense axis by downregulating GPX4 and SLC7A11 expression, thus inducing ferroptosis. Further investigations confirmed the therapeutic efficacy of Exosome-UIOFs in human-derived glioma xenograft mouse models, resulting in substantial inhibition of intracranial tumor growth and prolonged survival in tumor-bearing mice. This study presents an innovative strategy for the development of exosome and ultrathin iron oxide framework-based therapeutics for glioma treatment.[101]

Liu et al developed a magnetite nanoparticle (MNP)-based catalytic nanoreactor, CMNP-Cis-Arg, designed to promote ferroptosis in glioblastoma (GBM) cells. CMNP-Cis-Arg facilitates targeted GBM delivery via GLUT1-mediated blood-brain barrier (BBB) penetration and arginine-driven chemotaxis towards tumor sites. This nanoreactor not only enhances lipid oxidation in GBM cells but also induces ferroptosis through the generation of reactive oxygen species (ROS) and the depletion of intracellular glutathione (GSH). The MNPs within the nanoreactor amplify the Fe^{2+}-mediated Fenton reaction, while cisplatin, as a chemotherapeutic agent, induces DNA strand breaks, further depleting GSH and increasing ROS levels. Moreover, CMNP-Cis-Arg promotes lipid oxidation by generating highly reactive peroxynitrite ($ONOO^-$), which accelerates ferroptosis. This study demonstrates the significant induction of GBM cell apoptosis both in vitro and in vivo, and notably reduces tumor burden in mouse xenograft models. The results highlight the potential of this catalytic ferroptosis nanoreactor as an innovative therapeutic strategy for GBM, warranting further preclinical investigation.[102]

Kangli Xue et al developed a novel near-infrared (NIR) light-responsive nanoplatform, ApoE-UMSNs-GOx/SRF, to enhance ferroptosis therapy for glioblastoma (GBM). This platform is constructed using upconversion nanoparticles (UCNPs), sequentially coated with a mesoporous silica layer and a lipid bilayer, which is loaded with glucose oxidase (GOx) and sorafenib (SRF), and further functionalized with ApoE peptides for efficient BBB penetration and GBM targeting. The findings indicate that ApoE-UMSNs-GOx/SRF accumulates effectively at the GBM site and induces enhanced ferroptosis upon NIR irradiation. The UCNPs facilitate the conversion of NIR light into ultraviolet light, thereby reducing Fe^{3+} to Fe^{2+}, while GOx catalyzes the generation of excess H_2O_2 through glucose oxidation. This combination of processes significantly elevates ROS production. In parallel, SRF inhibits the Xc^- system, leading to the accumulation of lipid peroxides and reinforcing anti-glioma effects. This strategy holds promise for improving the therapeutic efficacy of ferroptosis as a treatment for GBM.[84]

Shao et al developed a novel nanocomposite, ApoE-UPGs-DHA, designed to enhance ferroptosis in glioblastoma cells. ApoE-UPGs-DHA was synthesized by co-loading upconversion nanoparticles (UCNPs) and dihydroartemisinin (DHA) into micelles, followed by functionalization with ApoE peptides to facilitate BBB penetration and targeted glioblastoma therapy. Under near-infrared (NIR) irradiation, ApoE-UPGs-DHA promotes the regeneration of Fe^{2+}, thereby enhancing ferroptosis in G422 glioma cells. This nanocomposite demonstrated excellent glioblastoma-targeting capabilities and exhibited substantial anti-tumor activity both in vitro and in vivo. Mechanistic studies revealed that ApoE-UPGs-DHA significantly promotes lipid peroxidation (LPO) via Fenton-like reactions, facilitated by NIR-induced reduction of endogenous Fe^{3+} to Fe^{2+}, which further enhances ferroptosis. This work presents a promising approach for the development of glioblastoma therapies based on iron regeneration mechanisms.[82]

Biomimetic Nanoparticles

Biomimetic nanoparticles (BNPs), which replicate the structure and properties of natural entities, have found extensive applications in drug delivery, theranostics, and tissue engineering. These materials offer several advantages, including prolonged blood circulation time, specific binding capabilities, and reduced side effects.[103] BNPs retain the complex biological functionalities of cell membranes while also benefiting from the excellent physicochemical properties of

nanoparticles. These attributes enable BNPs to evade protein adsorption and phagocytosis by the reticuloendothelial system (RES), thereby facilitating prolonged circulation and targeted drug delivery.[104] Compared to conventional nanoparticles, biomimetic systems demonstrate superior stability, higher drug-loading capacity, and enhanced safety. Notably, BNPs exhibit improved targeting efficiency and reduced immune rejection, particularly in the treatment of glioblastoma (GBM).[105]

Liu et al designed a biomimetic, brain-targeted drug delivery system (Fe_3O_4-siPD-L1@M-BV2) aimed at enhancing the efficacy of immunotherapy for drug-resistant gliomas through the promotion of ferroptosis. This system employs disulfide bonds to conjugate thiolated siPD-L1 with thiolated Fe_3O_4 nanoparticles, which are subsequently coated with microglial cell membranes (M-BV2) to form biomimetic nanoparticles. In vivo experiments using a drug-resistant glioma mouse model demonstrated that this system significantly increased the accumulation of siPD-L1 and Fe^{2+}, reduced PD-L1 protein levels, and enhanced the effector T cell-to-regulatory T cell ratio. Furthermore, it induced ferroptosis in tumor cells, promoted dendritic cell maturation, and shifted the M1-to-M2 microglial ratio. As a result, Fe_3O_4-siPD-L1@M-BV2 effectively inhibited the growth of drug-resistant gliomas and prolonged survival in experimental animals. This study highlights the synergistic effects of ferroptosis and immune response activation, offering a promising therapeutic strategy for the treatment of drug-resistant gliomas.[74]

Cao et al developed a novel macrophage membrane-camouflaged nanocarrier (MMsaNPs) to induce ferroptosis in glioblastoma (GBM) cells by exacerbating mitochondrial damage. Through genome-wide CRISPR-Cas9 screening, the researchers identified ALOX15 as a key regulator of ferroptosis. Small activating RNA (saRNA) was subsequently employed to upregulate ALOX15 expression, promoting ferroptosis in GBM cells. Mesoporous polydopamine (MPDA), loaded with saALOX15, was then coated with Angiopep-2-modified macrophage membranes to mitigate clearance by the mononuclear phagocyte system and enhance blood-brain barrier (BBB) penetration. The resulting composite nanoparticles triggered ferroptosis by inducing mitochondrial dysfunction and morphological abnormalities. In vivo studies demonstrated that the engineered macrophage membrane enabled precise targeting of GBM cells, significantly slowing tumor progression and enhancing radiotherapy sensitivity. These findings underscore the therapeutic potential of ALOX15 in GBM treatment and present a biomimetic macrophage membrane-based approach to improve nanomaterial performance in GBM therapy.[88]

Wang et al developed an innovative nanoplatform, DOX-FN/C6M-NVs, for glioma treatment. This platform integrates nano-vesicles (NVs) derived from C6 glioma cell membranes (C6M), ultrasmall iron nanoparticles (FN), and the chemotherapeutic agent doxorubicin (DOX). Utilizing nanozyme-mimicked peroxidase activity, the platform suppresses tumor growth by enhancing the ferroptosis pathway. These nanozymes effectively penetrate the BBB and specifically target tumor sites, demonstrating excellent anti-tumor efficacy in vivo models. By inducing mitochondrial damage in tumor cells and increasing reactive oxygen species (ROS) levels, nanozymes promote ferroptosis. Further in vivo validation in xenograft glioma mouse models showed that this nanozyme-controlled system significantly reduced intracranial tumor volume and prolonged survival. This work paves the way for the development of novel glioma therapies based on nanozyme technology.[75]

Zhu et al introduced a novel biomimetic nanosonosensitizer, PIOC@CM NPs, specifically designed for in situ glioma treatment. Composed of Fe_3O_4 and Ce6, PIOC@CM NPs can safely and transiently open the BBB when exposed to ultrasound (US) in combination with circulating microbubbles (MBs), exhibiting high tumor selectivity and potent anti-tumor effects. Upon ultrasound exposure, this nanosonosensitizer significantly enhances ROS production while depleting glutathione (GSH), leading to the inactivation of glutathione peroxidase 4 (GPX4) and promoting a synergistic effect of sonodynamic therapy (SDT) and ferroptosis in tumor cells. In vivo studies on glioma mouse models demonstrated that this strategy significantly inhibited tumor growth and improved survival rates. This research proposes an innovative approach combining non-invasive BBB opening, SDT, and ferroptosis induction, offering a promising new strategy for glioma treatment.[106]

Polymeric Nanoparticles

Polymeric nanoparticles are nanocarriers with sizes ranging from 1 to 1000 nanometers, which can take the form of nanocapsules or nanospheres. Renowned for their excellent biocompatibility and tunable surface properties, these

materials are considered highly promising for applications in drug delivery, diagnostic imaging, and therapeutic interventions.[107,108] These nanoparticles consist of polymers formed by the covalent bonding of one or more monomer units, resulting in linear or branched macromolecular structures. Natural polymers include polysaccharides (eg, hyaluronic acid), proteins (eg, albumin), peptides, and nucleic acids, whereas synthetic polymers are chemically engineered materials, such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polylactic acid (PLA), polyglycolic acid (PGA), and poly(ε-caprolactone) (PCL).[109] By leveraging the unique advantages of nanotechnology, polymeric nanoparticles can enhance drug penetration across the blood-brain barrier (BBB), increase drug concentrations at tumor sites, and extend circulation times through surface modifications, such as PEGylation. These capabilities highlight the considerable potential of polymeric nanoparticles for the treatment of malignant gliomas.[89]

Li et al designed an innovative targeted drug delivery system that utilizes the L-type amino acid transporter 1 (LAT1) as a target for glioma therapy. Through hydrothermal synthesis, they developed nanoparticles co-loaded with temozolomide (TMZ) and sorafenib, which demonstrated not only excellent penetration of the BBB but also significant anticancer efficacy. The experimental data revealed that this nanoparticle-based system facilitated LAT1-specific drug uptake in tumor cells, thereby enhancing cytotoxicity and accumulation in tumor regions, ultimately improving overall anticancer effectiveness. Furthermore, the study indicated that the ferroptosis mechanism induced by sorafenib could further potentiate the anti-glioma activity of TMZ. Both in vitro and in vivo experiments confirmed that these LAT1-targeted nanoparticles effectively inhibited tumor growth and prolonged survival in experimental animals, offering a novel approach for LAT1-mediated glioma treatment.[76]

Fan et al developed a novel matrix metalloproteinase-2 (MMP-2)-sensitive nanomaterial (S-biAb/dEGCG@NPs) designed to enhance ferroptosis and support glioblastoma (GBM) immunotherapy. This nanostructure incorporates bispecific antibodies (biAbs) targeting the B7-H3 molecule and is synthesized via hydrothermal methods, exhibiting exceptional tumor localization and responsiveness to tumor microenvironmental changes. In an MMP-2 enzyme-rich tumor environment, S-biAb/dEGCG@NPs enable the sustained release of biAbs, promote T-cell infiltration, and activate ferroptosis while simultaneously blocking immune checkpoints. In vitro and in vivo experiments demonstrated that S-biAb/dEGCG@NPs significantly enhanced the therapeutic efficacy against GBM, with half of the treated mice surviving for over 56 days. These results position S-biAb/dEGCG@NPs as an efficient antibody delivery platform with substantial potential to augment comprehensive cancer therapies.[77]

Ding et al engineered a neutrophil-based "Trojan Horse" nanotherapy system (SPCFe/siP) for ultrasound-activated ferroptosis-immunotherapy combination treatment against primary gliomas. This system utilizes neutrophils to cross the BBB and deliver drugs precisely to the target lesion. SPCFe/siP comprises a semiconductor polymer, PD-L1 siRNA, and Fe_3O_4 nanocrystals encapsulated within a nanocarrier that is cleavable by singlet oxygen ($^1O_2$) and decorated with sialic acid ligands for specific recognition by neutrophils. Upon ultrasound stimulation, the semiconductor polymer generates $^1O_2$, triggering the decomposition of the nanocarrier and the release of Fe_3O_4 nanocrystals and PD-L1 siRNA. The Fe_3O_4 nanocrystals induce ferroptosis and subsequent immunogenic cell death (ICD), while PD-L1 siRNA downregulates PD-L1 expression on tumor cells, thereby synergistically enhancing the therapeutic efficacy of ultrasound-activated ferroptosis and immune modulation. In vivo experiments demonstrated that this strategy effectively controlled glioma growth in a mouse model and improved survival outcomes. This study introduces an innovative and efficient neutrophil-guided nanodelivery system, with broad potential applications in brain disease therapy.[110]

Hybrid Nanoparticles

Hybrid nanoparticles are nanostructures formed by combining polymers with inorganic or organic matrices, encompassing components such as metal oxide nanoparticles, graphene, carbon nanotubes, silica, and various polymers as inorganic materials, as well as phospholipids, proteins, and lipids as organic constituents.[111] In comparison to non-hybrid systems, these composite nanoparticles offer a range of advantages, including prolonged blood circulation, reduced premature drug leakage, enhanced encapsulation efficiency, and optimized non-specific release mechanisms.[90] In the context of biomedical applications, hybrid nanoparticles play a crucial role, particularly in drug delivery, gene therapy, bioimaging, disease diagnostics, and therapeutic interventions. They enable controlled and sustained drug release at targeted regions,

effectively shield active compounds from external environmental degradation, and minimize the risk of adverse reactions.[112] Numerous studies have reported on hybrid nanoparticles specifically engineered for the treatment of glioma.[113–115]

Zhang et al introduced an innovative 3D-printed hydrogel-liposome nanoparticle platform (T+E@LPs-cRGD +GelMA) designed to prevent glioma recurrence. This platform integrates cross-linked gelatin hydrogel with cRGD-modified liposomes, demonstrating excellent biocompatibility and sustained drug release properties. The study showed that T+E@LPs-cRGD+GelMA can precisely target tumor cells, significantly reducing O-6-methylguanine-DNA methyltransferase (MGMT) levels and increasing the expression of the tumor-suppressor protein p53. Transcriptomic analysis revealed that this nanoparticle system promotes ferroptosis by inducing the accumulation of intracellular reactive oxygen species (ROS) and lipid peroxidation, thereby overcoming drug resistance. In vivo experiments further validated the efficacy of T+E@LPs-cRGD+GelMA in inhibiting intracranial tumor growth and extending survival in murine models. This research paves the way for the development of novel hydrogel-liposome composite systems for glioma therapy.[78] Hao et al designed a novel hybrid nanocarrier (hNRVs) to enhance the synergistic effects of ferroptosis and immunotherapy in glioma treatment. These nanoparticles consist of exosomes derived from natural killer (NK) cells, which are combined with liposomes loaded with the ferroptosis inducer RSL3. Exploiting the tumor-targeting capability and enhanced permeation and retention (EPR) effects of NK cell-derived exosomes, hNRVs achieve efficient accumulation and cellular uptake at tumor sites. Upon entry into the tumor microenvironment, hNRVs release FAS ligand (FASL), interferon-gamma (IFN-γ), and RSL3. FASL induces tumor cell lysis, while RSL3, a GPX4 inhibitor, induces ferroptosis in tumor cells. Concurrently, the increased levels of IFN-γ and tumor necrosis factor-alpha (TNF-α) activate dendritic cells, leading to GPX4 inactivation and promoting lipid peroxidation, thereby sensitizing the tumor to ferroptosis. The study demonstrated that this customized hNRV platform enhances overall therapeutic efficacy by selectively delivering ferroptosis inducers and immune activators without imposing additional burdens on healthy organs, offering a novel approach for clinical applications and future research in glioma treatment.[116]

Self-Assembled Nanoparticles

Self-assembled nanoparticles are stable structures that spontaneously form through non-covalent interactions between individual components, exhibiting properties and functionalities that are distinct from those of the constituent materials.[117] In drug delivery systems, these nanoparticles offer remarkable advantages, particularly in cancer therapy. They can be surface-modified to enable precise targeting of specific regions, effectively protect encapsulated drugs from degradation, and release them in response to specific environmental stimuli, such as those found in the tumor microenvironment. These features not only enhance therapeutic efficacy but also minimize adverse side effects. Furthermore, due to their straightforward preparation, multifunctionality, and exceptional biocompatibility, self-assembled nanoparticles are considered powerful tools for improving the effectiveness of anticancer therapies.[118,119] Notably, in the context of glioma treatment, these nanomaterials demonstrate significant clinical application potential. Constructed from naturally occurring bioactive substances and held together by non-covalent bonds, they not only improve the solubility of poorly soluble drugs but also facilitate the crossing of the blood-brain barrier (BBB) and enhance drug concentration within tumor cells through targeted delivery mechanisms, thereby boosting overall therapeutic efficacy.[120,121]

Zhu et al developed a novel carrier-free self-assembled nanosonosensitizer (Ce6@Cu NPs) designed to enhance both cuproptosis and ferroptosis in the treatment of glioma. This nanosonosensitizer forms through the coordination of Cu^{2+} with chlorin e6 (Ce6) and generates singlet oxygen ($^1O_2$) upon ultrasound irradiation, disrupting copper and iron metabolism within glioma cells. In experiments with U87MG cells, Ce6@Cu NPs, activated by ultrasound-induced sonodynamic effects, significantly reduced glutathione (GSH) levels, leading to the inactivation of glutathione peroxidase 4 (GPX4), promoting lipid peroxidation (LPO), and ultimately triggering ferroptosis. Concurrently, the reaction between Cu^{2+} and GSH resulted in elevated Cu^{+} levels, impairing mitochondrial function and further inducing cuproptosis. Importantly, these nanoparticles demonstrated effective penetration of the blood-brain barrier and favorable tumor accumulation in an in situ U87MG-Luc glioma model. Both in vitro and in vivo experiments confirmed that Ce6@Cu NPs effectively inhibited tumor growth by simultaneously activating ferroptosis and cuproptosis mechanisms, with

minimal side effects. This study paves a novel pathway for glioma treatment by combining cuproptosis and ferroptosis strategies.[80]

Zhao's research team developed a graphene diacetylene (GDY)-based nanoparticle platform (GFR) for combined photothermal and ferroptosis therapy in glioblastoma (GBM). The GFR nanoplatform utilizes self-assembly to load the ferroptosis inducer FIN56 onto GDY and is further modified with RAP peptide to enhance its ability to cross the blood-brain barrier. GFR efficiently loads FIN56 in a pH-dependent manner, promoting its release in acidic environments. Under 808 nm laser irradiation, GFR significantly increases the local temperature and accelerates FIN56 release, thereby enhancing ferroptosis induction in GBM cells. Experimental results demonstrated that GFR induces ferroptosis in GBM cells by inhibiting GPX4 expression, effectively controlling tumor growth and prolonging survival in a GBM xenograft mouse model. Moreover, 808 nm laser treatment further augmented the therapeutic efficacy of GFR-mediated therapy. This study highlights the potential of GDY-based nanomaterials for GBM treatment and underscores the promise of combining photothermal therapy with ferroptosis for the treatment of GBM.[81]

Liang et al developed a brain-targeted self-assembled nanoparticle platform based on drug repurposing to enhance ferroptosis therapy for glioblastoma (GBM). They loaded the antimalarial drug dihydroartemisinin (DHA) and the photosensitizer indocyanine green (ICG) onto lactoferrin (LF) to form the L-D-I/NPs complex. This nanocarrier specifically targets glioma cells by recognizing the low-density lipoprotein receptor-related protein-1 (LRP1) and effectively crosses the blood-brain barrier. L-D-I/NPs induce ferroptosis in glioma cells by increasing intracellular reactive oxygen species (ROS) levels and promoting iron accumulation. Animal experiments further confirmed that L-D-I/NPs effectively inhibited glioma progression in situ and significantly improved survival rates in experimental mice. This innovative nanoparticle platform facilitates the use of non-traditional anticancer drugs while reducing associated side effects, offering a novel approach for more effective ferroptosis-based glioma treatment.[122]

Outlook

Revisions:Nanoparticles offer significant advantages in the treatment of glioma. Through specific surface modifications, these nanoparticles can selectively target and bind to tumor cells with high precision, thereby minimizing damage to healthy tissues. Additionally, they enable the slow and controlled release of therapeutic agents, enhancing overall treatment efficacy. This technology provides an innovative strategy for overcoming the blood–brain barrier (BBB), a major obstacle in the treatment of central nervous system (CNS) malignancies, including gliomas.

This review summarizes recent advances in nanotechnology for glioma therapy based on the ferroptosis mechanism. Inorganic nanoplatforms such as Fe_3O_4 nanoparticles induce oxidative stress via the Fenton reaction, while biomimetic carriers enable triple-targeted delivery, and hybrid systems help overcome chemoresistance. Multimodal synergistic therapies—combining sonodynamic, photothermal, and immunotherapy—have been shown to significantly prolong survival. However, clinical translation faces three primary challenges: biosafety, barrier penetration, and efficacy evaluation. Addressing these requires the development of biodegradable carriers and dynamic monitoring systems.Innovatively, this review proposes a molecular mapping of the ferroptosis pathway and a spatiotemporally sequenced therapeutic paradigm, offering theoretical support for the development of precision treatment strategies and advancing the transition from basic research to clinical application. Nevertheless, several issues must be addressed to enable successful clinical translation of nanoparticle-based therapies, including biocompatibility, long-term toxicity, material stability, drug release efficiency, production costs, dosage control, and regulatory compliance.

Future research should focus on several key areas: first, the development of novel nanomaterials that enhance therapeutic efficacy while minimizing adverse reactions; second, a deeper exploration of the molecular mechanisms underlying ferroptosis to provide a more robust theoretical foundation for drug development; third, the investigation of potential synergistic effects by combining nanoparticles with other therapeutic modalities; and finally, the expansion of clinical trials to rigorously evaluate the safety and efficacy of nanoparticle-based therapies. Through

these efforts, ferroptosis-based nanoparticle therapies have the potential to emerge as a pivotal strategy in the fight against glioma.

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