

Application of Multifunctional Metal Nanoparticles in the Treatment of Glioma

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Abstract: Glioma is the most common primary malignant brain tumor with a poor survival rate. It is characterized by diffuse and invasive growth and heterogeneity, which limits tumor identification and complete resection. Therefore, the precise detection and postoperative adjuvant therapy of gliomas have become increasingly important and urgent. Nanotechnology, with its excellent biocompatibility and controllable chemical properties, has attracted much attention in recent decades. Metal nanoparticles are widely used in the field of biomedical imaging and detection, and have shown promising applications in targeted drug delivery and therapy. The current review aims to systematically summarize the application of different types of metal nanoparticles in the treatment and detection of glioma. We also discussed the advantages and mechanisms of metal nanoparticles when used for glioma therapy, including chemotherapy, radiotherapy and photothermal therapy. We hope to promote the application of metallic nanoparticles in glioma diagnosis and treatment, moving towards clinical translation to benefit patients.

Keywords: metal nanoparticles, glioma, treatment

Introduction

Despite tremendous development in biomedical technology, malignant brain gliomas has been one of the most malignant and aggressive diseases, posing an extremely serious threat to human survival. Since the 21st century, the mortality rate of brain gliomas has risen significantly in the world.¹ Most malignant brain gliomas are treated with maximum safe aggressive surgery followed by adjuvant therapy, eg chemotherapy and radiotherapy.^{2,3} Numerous studies are trying to overcome obstacles in the treatment and detection of glioma.⁴ However, the inherent aggressive growth of malignant glioma results in limited therapeutic efficacy.

Based on the molecular pathology of glioma, these tumors are classified as astrocytoma, oligodendroglioma or glioblastoma (GBM) according to WHO.⁵ GBM is the most aggressive form of glioma, its cell density and nuclear atypia are significantly increased, with multi nuclear fission and pathological mitosis, showing obvious endovascular hyperplasia and necrosis.⁶ After undergoing surgical resection, it is inevitable that there will be local residual tumor micro-infiltration and recurrence. In addition, radiotherapy resistance and chemotherapy resistance are prominent problems encountered in GBM treatment.⁷ Therefore, GBM remains one of the most difficult tumor to treat and the median survival time of GBM patients is less than 14.6 months.^{8,9} It is urgently needed to develop new methods to combat glioma and improve the life quality and survival time of patients.

Nanotechnology is an emerging field that has made huge advances in biomedicine and shown promising prospects in clinical trials for cancer treatment, detection, and precise targeted therapy (Table 1). Metal nanoparticles offer an unprecedented opportunity to revolutionize and invent novel detection methods for gliomas or to boost the effectiveness of therapy.¹⁰ They possess several unique properties, thereby establishing a prominent position in the field of drug delivery system. First, metal



Table 1 Clinical Trials of Nanomaterials in Brain Cancers

Nano Agents	Brain Tumor	NCT ID	Phase	Status	Refs
Liposomal-Irinotecan	Recurrent high-grade glioma	NCT02022644	I	Completed	[13,14]
MTX110	Newly diagnosed diffuse intrinsic pontine glioma	NCT03566199	II	Completed	[15]
ABI-009	Recurrent high-grade glioma and newly diagnosed glioblastoma	NCT03463265	II	Completed	
MTX110	Newly diagnosed diffuse midline gliomas	NCT04264143	I	Completed	[15]
Nanoliposomal CPT-11	Recurrent high-grade gliomas	NCT00734682	I	Completed	[16]
AGuIX Nanoparticles	Newly diagnosed glioblastoma	NCT04881032	II	Recruitment	[17]
INCMGA00012 and Epcadostat	Recurrent gliomas	NCT03532295	II	Active, not recruitment	
EGFR(V)-EDV-Dox	Recurrent glioblastoma	NCT02766699	I	Unknown status	
Irinotecan Liposome	Diffuse intrinsic pontine glioma	NCT03086616	I	Completed	[18]
NL CPT-11	Recurrent high-grade gliomas	NCT00734682	I	Completed	[19]
Rhenium Nanoliposomes	Recurrent glioma	NCT01906385	II	Recruitment	[20]
RNA-lipid Particle	Newly diagnosed pediatric high-grade gliomas and adult glioblastoma	NCT04573140	I	Recruitment	[21]
Vaccines					
Pegylated Liposomal Doxorubicin and Prolonged Temozolomide	Newly diagnosed glioblastoma	NCT00944801	II	Completed	[22]
Liposomal verteporfin	Recurrent high-grade EGFR-mutated glioblastoma	NCT04590664	I, II	Recruitment	[23]
AGuIX® Nanoparticles	Brain metastases	NCT04094077	II	Terminated	[24,25]
AGuIX Gadolinium Based Nanoparticles	Brain metastases	NCT02820454	I	Completed	[24,25]
AGuIX®	Multiple brain metastases	NCT03818386	II	Active, not recruiting	[24,25]
Liposomal Cytarabine	Central nervous system metastases from breast cancer	NCT00992602	II	Completed	[26]
Nal-IRI	Brain metastases in breast cancer	NCT03328884	II	Active, not recruitment	[27,28]
MM-398 (Nanoliposomal Irinotecan, Nal-IRI)	Metastatic breast cancer with active brain metastasis	NCT01770353	I	Completed	[27,28]
NU-0129 (SNA gold nanoparticle)	Recurrent glioblastoma or gliosarcoma undergoing surgery	NCT03020017	I	Completed	[29]

nanoparticle drugs not only exhibit improved absorption and enhanced bioavailability in vivo, but also offer potential advantages in pharmacokinetics, biocompatibility, and controlled degradability. Second, metal nanoparticles reach GBM sites through both passive and active targeting mechanisms. They can also accumulate at tumor sites through the enhanced permeability and retention (EPR) effect in passive targeting. Additionally, surface modifications and targeting ligands enable active targeting to specific tumor cells.¹¹ Third, metal nanoparticles present an advantage in tumor target therapy. They not only provide improved specificity and increased sensitivity for medical imaging detection.¹² All of these properties contribute to the future treatment and detection of glioma.

In this review, we will firstly introduce different types of metal nanomaterials, including gold nanoparticles, magnetic iron oxide nanoparticles and some metal-based quantum dots, illustrating advantages of nanoparticles in the treatment and detection of glioma. Secondly, we will reveal the capacity of metal nanoparticles in drug delivery, tumor target therapy and detection of malignant glioma. Finally, we will explore the mechanisms of metal nanoparticles in glioma imaging as well as the application of nanotechnology in radiotherapy, chemotherapy, and photothermal therapy.

Different Types of Metal Nanoparticles in Glioma Therapy

Since liposomes were first used in the biomedical field, a large number of nanoparticles have been approved by the FDA for medical applications.¹³ Nanoparticles are defined as ultrafine particles, the size of which is in the range of 1–100 nm. These small size nanoparticles have a good ability to cross the Blood-Brain Barrier (BBB) without causing damage to normal tissues.¹⁴ Recently, metal nanomaterials are becoming increasingly important in the field of medical imaging and cancer treatment. The excellent biocompatibility and drug delivery capability of the metal nanomaterials make them to possess a promising future in the controlled drug release, cancer detection, drug delivery and tumor therapy. Actually,

metal nanoparticles have been used in tumor diagnosis and treatment for decades.¹⁵ Since the 1990s, magnetic nanoparticles have been utilized for imaging detections and have been combined with various other contrast agents for the diagnosis of liver cancer.¹⁶ Many noble metal nanoparticles,¹⁷ such as gold and silver, are widely used in tumor radiotherapy, drug loaded chemotherapy, photothermal treatment and immunotherapy.¹⁸

Additionally, metal nanoparticles are involved in glioma resistance to therapies, with the PI3K/AKT, MAPK, and NF- κ B signaling pathways contributing to this resistance.¹⁹ To overcome this resistance, current strategies focus on improving therapeutic efficacy and targeting the underlying resistance mechanisms, including selective inhibition of critical signaling pathways (eg PI3K/AKT, MAPK), combination with other treatment modalities,^{20,21} the use of functionalized nanoparticles for precise targeting,^{22,23} integration with gene therapy,²⁴ and immune system modulation.²⁵

In this chapter, we will not only introduce different types of metal nanoparticles, including noble metal nanoparticles, metal quantum dots, metal oxide nanoparticles, but also review their unusual advantages of nanotechnology in glioma treatment.

Noble metal nanoparticles

Noble metal nanoparticles include gold, silver, and platinum.²⁶ These nanoparticles have good water dispersion and biocompatibility, they can effectively accumulate in the tumor site and have a long internal circulation time. Therefore, noble metal nanomaterials are considered as excellent CT contrast agent.^{27,28} For example, gold nanoparticles (Au NPs) have been widely studied and used in biomedical applications.²⁹ Different shapes of gold nanostructures have been prepared, including gold spheres, gold rods, gold shells and gold cages.³⁰ On the other hand, high Z metals are capable to deposit radiation energy and produce a series of secondary electrons, such as Compton electrons and Auger electrons. These electrons can either directly damage DNA of tumor cells or react with water, resulting in the generation of reactive oxygen species (ROS). This process may enhance the anti-tumor effect.^{31,32} Therefore, high Z metal nanoparticles can accumulate in the tumor area through the EPR effect, absorbing radiation energy, and sensitizing the effect of radiotherapy. Liu et al found that silver nanoparticles (Ag NPs) could enhance the radiotherapy efficacy in hypoxic glioma cells through promoting cell apoptosis and enhancing destructive autophagy.³³ Nowadays, high Z metal nanoparticles have introduced a new therapeutic approach for GBM.³⁴ Following chemical innovations with temozolomide, an alkylating agent, and subsequent biological innovations utilizing humanized IgG1 monoclonal antibody like bevacizumab, which targets all isoforms of VEGF-A, the first generation of nanoparticles has been developed. These nanoparticles aim at optimizing drug delivery and controlling the release rate of medications such as doxorubicin (Figure 1). Therefore, high Z metal nanoparticles have shown potential application value in the diagnosis and treatment of glioma.

Metal oxide nanoparticles

Metal oxide nanoparticles and sulfide nanoparticles have higher chemical reactivity and unique physical properties due to its small size and large surface area. In general, metal oxide nanoparticles have the following advantages in the application of cancer treatments. First, the chemotherapy drugs, when loaded with metal oxides or their hybrid nanoparticles, such as Fe₃O₄ nanomaterials, have the potential to accumulate within the tumor core.^{35,36} This selectivity targets and kills tumor cells, with less side effects on normal tissue. Second, metal oxide nanoparticles can induce tumor cell apoptosis by generating ROS, which plays an important role in the damage of cancer cells. Third, metal oxide nanoparticles are significant for radiotherapy due to their enhanced action of sensitization and ionization. Owing to the advantages of metal oxide nanoparticles, their primary applications include magnetocaloric therapy, magnetic targeting therapy and magnetic resonance imaging. Photothermal therapy with metal nanoparticles can accelerate the speed of the blood circulation in tumor vessels and increase the amount of oxygen in the blood. Gu et al developed a new type of photosensitizer by combining photosensitive molecular porphyrin with iron oxide nanoparticles for photodynamic therapy and magnetocaloric therapy.³⁷ This photosensitizer can improve the hypoxic microenvironment, and further enhance the sensitivity of photodynamic therapy, ultimately achieving the optimal therapeutic effect. In addition, magnetic oxide nanoparticles also have potential applications in molecularly targeted therapy. By applying a high gradient magnetic field at specific external locations, magnetic nanoparticle drugs can be concentrated within tumor tissue and can be released by altering certain parameter^{38,39} (Figure 2).

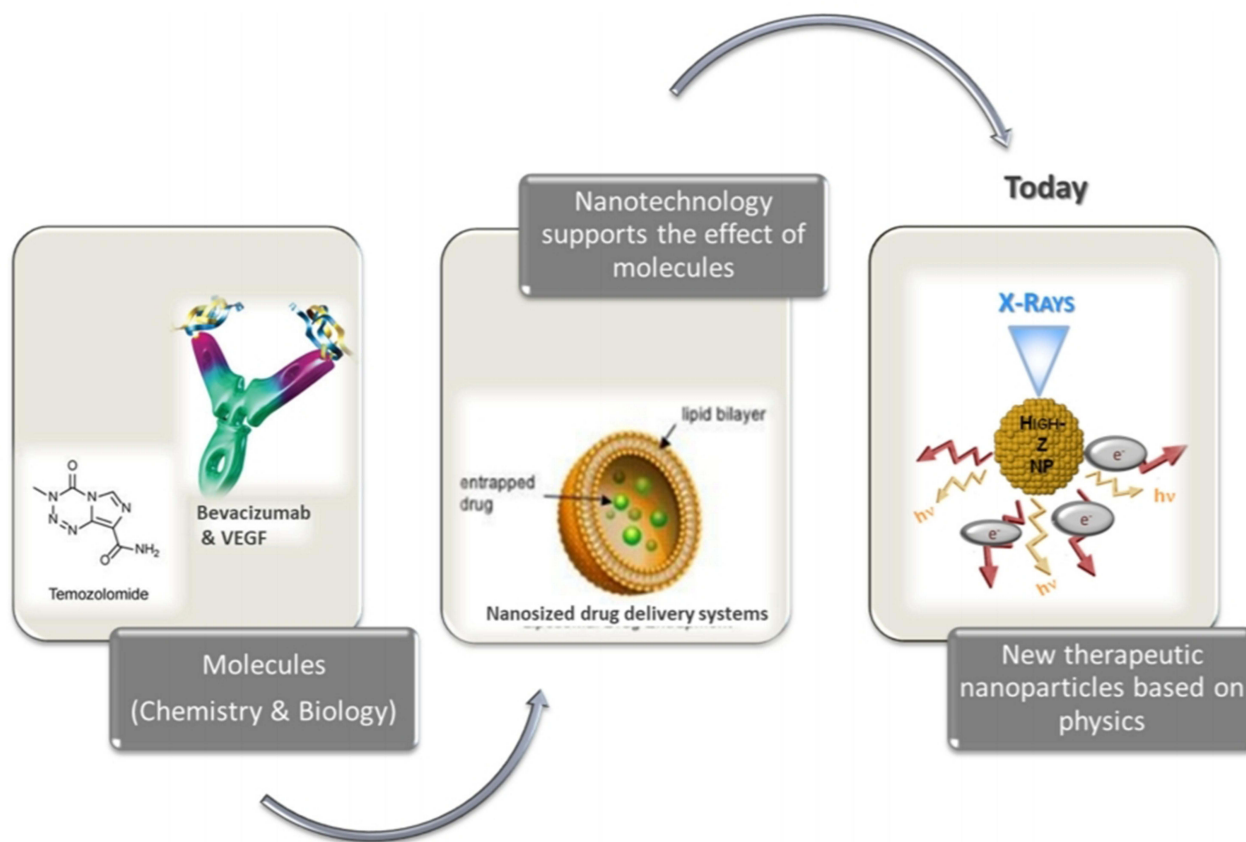


Figure 1 The development history of treating GBM with nanotechnology.

Note: Reprinted from Pinel S, Thomas N, Boura C, Barberi-Heyob M. Approaches to physical stimulation of metallic nanoparticles for glioblastoma treatment. *Adv Drug Deliv Rev.* 2019;138:344–357.³⁴

Sulfide nanoparticle, another kind of metal oxide nanomaterial, possesses high absorption coefficient and strong X-ray attenuation ability. These characteristics make the material, such as Bi_2S_3 use in photothermal therapy. Liu et al reported a nanodrug based on Bi_2S_3 nanorods. The Bi_2S_3 nanorods have ideal photothermal effect and enhanced imaging contrast under multispectral photoacoustic tomography and X-ray computed tomography image navigation. This nanomaterial can accurately target the tumor after intravenous injection, effectively inhibiting tumor growth and metastasis. In addition, the Bi_2S_3 nanorods have good biocompatibility.^{41,42} Taken together, sulfide nanoparticle could simultaneously enable precise cancer therapy and diagnosis monitoring.

Metal quantum dots

Quantum dots (QDs), also known as semiconductor nanocrystals, are inorganic semiconductor nanoparticles with small radius or close to the radius of exciton Bohr.⁴² Due to their special optical properties, the surface of QDs is easy to be functionalized with different ligands. QDs have potential application prospects in drug modification, affinity ligands, and medical imaging detection⁴³ (Figure 3). In particular, near infrared (NIR) fluorescent QDs can penetrate human tissues, and the fluorescence is rarely eliminated by metabolism in the human body, which makes QDs become a good in vivo imaging method.⁴⁴ Gao et al designed a multifunctional QDs probe capable of simultaneously targeting tumor cells and capturing biological imaging in vivo. They conducted preliminary research on the application of QDs.⁴⁵

The Advantages of Metal Nanoparticles

Firstly, the surface of metal nanoparticles can be modified with different kinds of ligand molecules, such as small molecule compounds, polymers, and biological macromolecules. Under certain conditions, these molecules can be self-

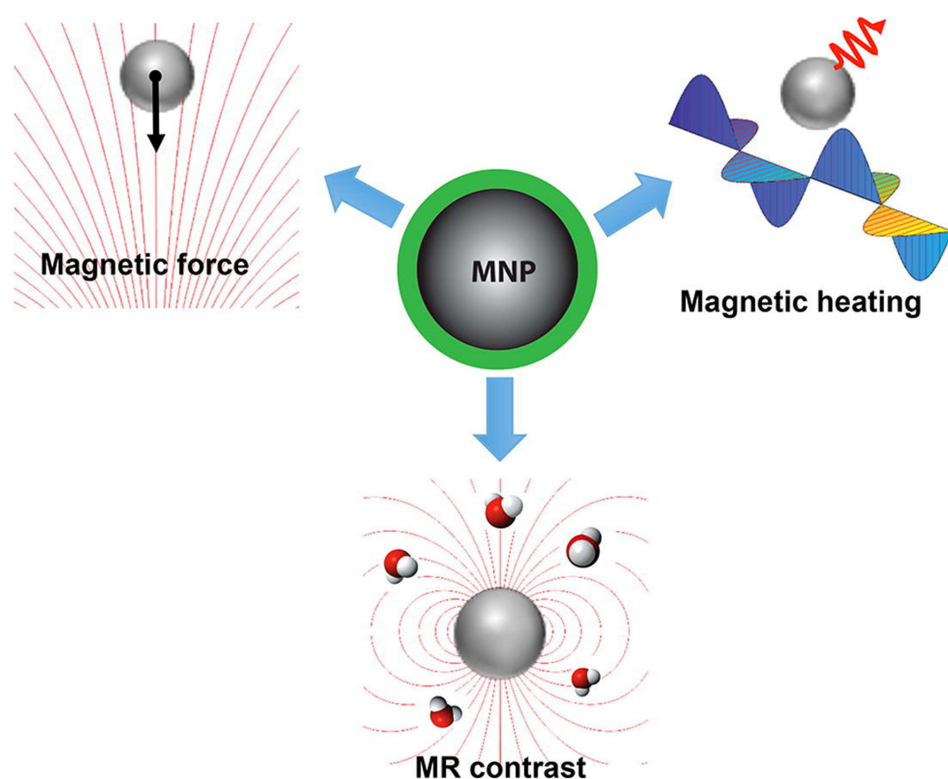


Figure 2 The applications of Magnetic nanoparticle (MNP) for disease detection and therapy.

Note: Reprinted from *Materials Today*, volume 31, Tong S, Zhu H, Bao G. Magnetic iron oxide nanoparticles for disease detection and therapy. 86–99, copyright 2019, with permission from Elsevier.³⁹

assembled or polymerized intelligently by changing hydrogen bonds, metal coordination, and electrostatic interaction. Polyethylene glycol, an amphiphilic molecule, is an ideal material for modifications. The hydrophobic end possesses a high affinity for nanoparticles, while the hydrophilic end can improve the water solubility of metal nanoparticles in liquid environment, thus reducing the toxicity of metal nanoparticles and improving the biocompatibility.⁴⁷ Tian et al reported a design using polyethylene glycol-lysine-oleic acid to encapsulate magnetic nanoparticles, which is expected to serve as a magnetic resonance imaging (MRI) contrast agent and also for cancer therapy.⁴⁸ Lai et al modified two groups of gold nanoparticles with chemical groups of *o*-nitrobenzyl alcohol and lipoic acid 4-aminomethylbenzylamine respectively. The photosensitive *o*-nitrobenzyl group was first photolyzed to an active nitrous intermediate under UV irradiation, which was then coupled with benzylamine-modified gold nanoparticles.⁵²

Secondly, metal nanoparticles can be aggregated into tumor tissue through the EPR effect.⁴⁹ Nanoparticles are cleared by lymphatic vessels in normal tissues, while in tumor tissues, these particles can reach the tumor sites due to leaky tumor vasculature and poor lymphatic drainage, known as the EPR effect.⁴⁰ Yu et al prepared gold nanoparticles that were modified with DNA and protected by α -cyclodextrin to realize selective aggregation of gold nanoparticles in tumor lesions through the EPR effect.⁵⁰ When the gold nanoparticles reach the tumor site, single stranded DNA is released from α -cyclodextrins, resulting in single chain complementary pairing.⁵¹

Thirdly, the surface of metal nanoparticles decorated with a variety of specific ligands is capable of recognizing tumor cells, thereby achieving active targeting function.^{46,53} Ag Seleci et al developed transferrin-modified magnetic iron oxide nanoparticles or QDs that allow for efficient dual imaging detection of glioma. These novel nanoparticles are not only beneficial for MRI, but also show great potential in active targeting effect.⁵⁴ Xu et al encapsulated magnetic iron oxide nanoparticles, QDs and cilengitide (CGT) into liposomes, and this nanoparticle can actively target gliomas under the action of magnetic field and improve cellular uptake efficiency of drugs.⁵⁵ In addition, the functionalized and chemically modified metal nanoparticles play a crucial role in minimizing direct contact between metals and normal cells, as well as biological tissues. This results in fewer side effects and enhanced biocompatibility.

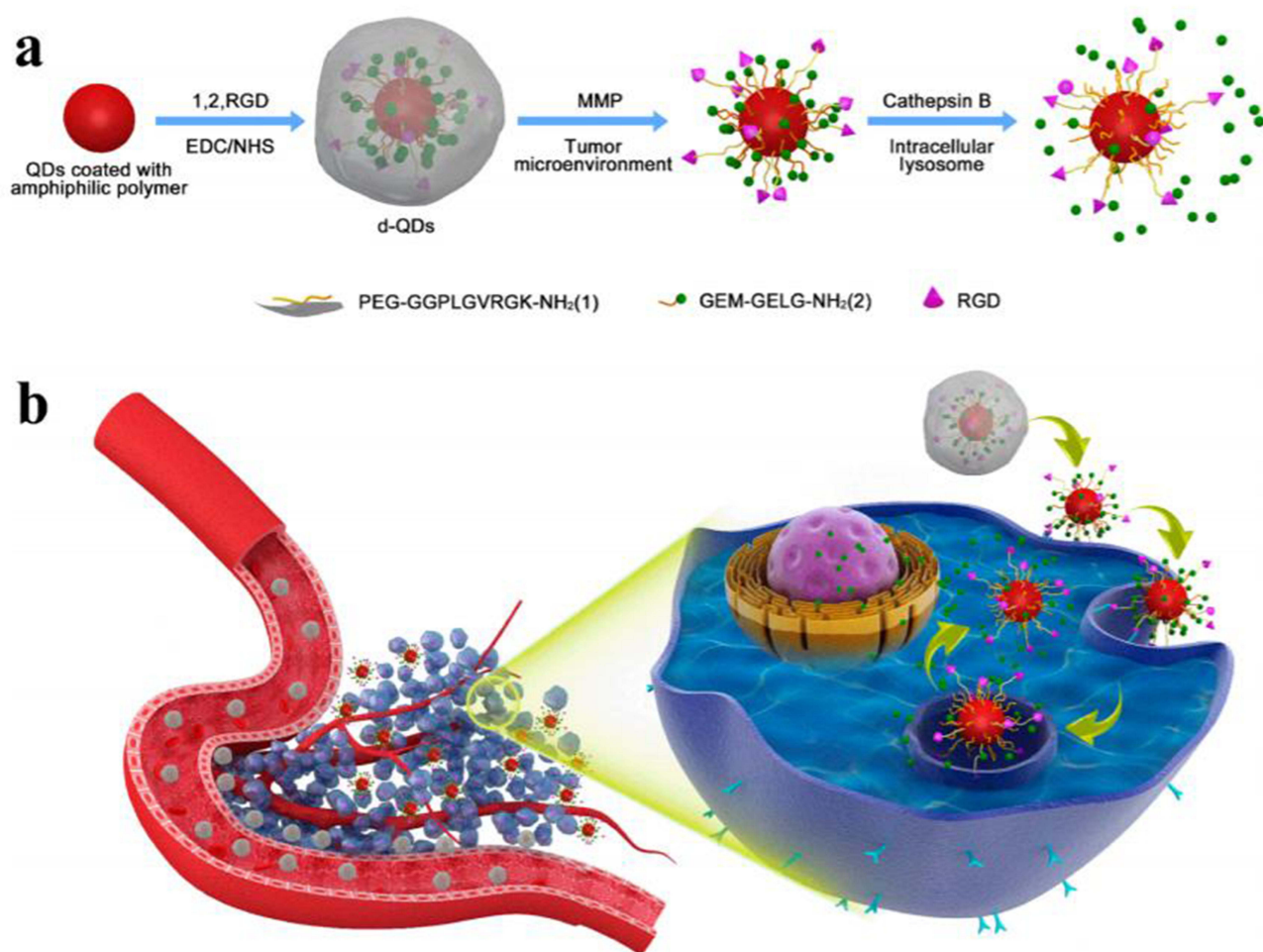


Figure 3 Quantum dots in drug delivery. (a) Schematic illustration of the nanovectors preparation protocol and their enzyme sensitive behavior. (b) Schematic illustration of the nanovectors delivering GEM to pancreatic cancer cells.

Note: Reprinted from Matea CT, Mocan T, Tabaran F, et al. Quantum dots in imaging, drug delivery and sensor applications. *Int j Nanomed.* 2017;12:5421–5431.⁴³

The Application of Metal Nanoparticles in Glioma Treatments Chemotherapy

Malignant brain tumors grow aggressively and rapidly infiltrate into surrounding tissues.^{56,57} The blurred boundary between malignant tissue and health tissue limits the effectiveness of surgery. Postoperative chemotherapy is a necessary adjuvant therapy to kill residual cancer cells. BBB is an important biological structure for the brain to resist harmful substances entering the brain tissue, such as bacteria, viruses and microorganisms. It is a structure between plasma and brain tissue composed of cerebrovascular endothelial cells, basement membrane, glial cells, pericytes and microglial cells. The tight connections between endothelial cells allow small molecules in plasma to enter the brain selectively. However, macromolecule chemotherapeutic, eg vincristine, can hardly cross the BBB. Moreover, conventional chemotherapeutic drugs also have bad influence on normal tissue and cause toxic side effects. Therefore, it is challenging for these drugs to accumulate in the tumor area due to the lack of specific targeting.

Owing to their unique physical and chemical properties, noble metal nanoparticles are designed as popular nano delivery system with targeting and responsive release abilities.^{58,59} Au NPs are readily adjustable in their particle size, and they not only have a larger specific surface area, but also offer flexibility for surface modification. For example, Au NPs show a strong affinity for the chemical reagent mercaptan, and these nanoparticles can be modified with various ligands such as polyethylene glycol (PEG) and oligonucleotides. Enhancing the time of blood circulation and

the stability of nanoparticles in the blood is advantageous.⁶⁰ Ruan et al designed a delivery system based on Au NPs. Au NPs were loaded with doxorubicin (DOX) by using an acid-reactive adaptor hydrazone. Angiopep-2, a specific ligand of low-density lipoprotein receptor associated protein-1 (LRP1), was used for nanoparticle functionalization. This nano delivery system can penetrate the BBB and target glioma cells, and thus realize precise chemotherapy. In vivo experiments showed that the modified nanoparticles can effectively prolong the median survival time of glioma-bearing mice. The Au NPs can also be decorated with PEG, allowing them to overcome the obstacle of BBB and enter the brain tumor area.⁶¹ Some Au NPs are coated with epidermal growth factor (EGF) peptides to kill cancer cells specifically. This type of nanoparticle protects EGF peptides from degrading in the blood and releases them into the slightly acidic microenvironment via the EPR effect, and also could minimize the toxic and side effects.^{62,63} The peptide sequence THRPPMWSPVWP, which interacts with transferrin receptor of the microvascular endothelial cell, was conjugated with Au NPs. This conjugation enhances the therapeutic effect.⁶⁴ Albertini et al injected Au NPs coated with arginine-glycine-aspartic acid-like peptide into the brain of mice. Two hours later, they observed that the number of peptide-modified nanoparticles aggregated in glioblastoma was 1.5 times higher than that of unmodified Au NPs.⁶⁵ These data demonstrate the great potential of the Au NPs delivery system in the treatment of brain tumors.

Recent advances in magnetic nanomaterials have shown promising prospects for improving MRI and treating tumors. These nanoparticles, usually in a small nanoscale, are widely used in the biomedical field. Magnetic nanoparticles (MNPs) play an important role in the targeted therapy of brain cancer. One of the most useful MNPs is the Fe₃O₄ nanoparticles.⁶⁶ Cole et al developed magnetic iron oxide nanoparticles modified with PEG. By applying an external magnetic field to the lesion area, these nanoparticles can help chemotherapy drugs accumulate in the tumor area.⁶⁷ This approach prolongs the circulation duration of nanodrugs within the body, demonstrating the efficacy of MNPs. Wu et al synthesized superparamagnetic iron oxide nanoparticles (SPION) that were coated with a silicate and carbon shell. The hydrothermal synthesis of these ferrofluid composite nanoparticles demonstrated a significant ability to inhibit the migration of glioma cells.⁶⁸ EGFR or mutant EGFRVIII was highly expressed in glioblastoma. Iron oxide nanoparticles coupled with the antibody against EGFR can effectively improve the targeting effect of chemotherapy drugs.⁶⁹ Overall, MNPs offers a promising platform for innovative drug delivery system and for optimizing the targeting strategies in brain tumor treatments.

To date, various QDs have been used for surface modification of nanoparticles to improve their stability, payload capacity and cellular uptake efficiency. Wahab et al found that QDs can inhibit tumor growth, reduce the invasiveness of glioma, and decrease the stemness of glioblastoma cells.⁷⁰ Mansur et al developed a ZnS QD biopolymer nanodrug system based on the method of host guest chemistry. The ZnS QDs were synthesized under normal pH physiological conditions, and then these QDs were chemically modified with carboxymethylcellulose (CMC) and polysaccharide. The chemotherapy drug DOX was electrostatically bound to the QDs. This newly formed supramolecular nanostructure can serve as an active fluorescent nanoprobe and a nano carrier for chemotherapy drugs, capable of controlling drug release and killing glioma cells.⁷¹ The further modification of QDs with targeted ligands can be used in the specific detection and treatment of glioma. Magnetic iron oxide nanoparticles and QDs modified with transferrin have been utilized for the treatment of glioma.⁵⁴

Radiotherapy

Radiotherapy refers to the use of one or more types of ionizing radiation to treat malignant tumors and some benign diseases, and it is an important adjunct therapy for malignant glioma.^{72,73} Malignant glioblastoma shows invasive growth, tends to invade the lobes and deep structures of the brain, and even invades the contralateral hemisphere through the corpus callosum. Although radiation therapy can compensate for the weakness of surgical resection, there are still a large number of patients who can not avoid cancer recurrence and metastasis after radiation therapy.⁷⁴ Moreover, it has some serious side effects because normal brain tissues can also be damaged by radiation. Therefore, researchers have been focusing on developing novel nanoparticles that are less harmful to healthy tissues and can boost the effectiveness of radiotherapy.

High atomic number (Z) metal nanoparticles have the ability to enhance ionization in their surroundings when exposed to ionizing radiation. Au NPs, which are high Z metal nanoparticles, have been shown to enhance the effect of

radiotherapy in gliomas.⁷⁵ Several mechanisms are involved in the sensitization effect of Au NPs in radiotherapy. Radiation can generate low-energy secondary electrons, trigger free radical effects, and cause indirect damage to DNA by assaulting its bases, demolishing ribose, and degrading oligonucleotide.^{76,77} In addition, radiation has the potential to harm biological membranes and proteins via lipid peroxidation. The Au NPs, characterized by high electron density, can effectively enhance the average cross section between tissue and radiation when they accumulate in tumor tissue to a certain extent. This accumulation improves the transfer and deposition of the physical dose of radiation during irradiation.

Au NPs are widely used in low dose radiotherapy because of their unique optical properties, good biocompatibility and excellent radiation sensitization. They can convert light energy into heat energy, showing a photothermal effect. This effect further enhances the efficacy of radiotherapy for gliomas. Kefayat et al designed a gold nanocluster modified with folic acid and bovine serum protein (BSA), named FA-AuNCs. Compared with traditional gold nanoparticles, these nanoparticles can specifically target C6 glioma cells and enhance the sensitivity of radiotherapy.⁷⁸ In addition, gold nanoparticles can effectively overcome the obstacle of BBB.⁷⁹ Ultra-small gold nanoparticles coated with gadolinium chelates (Au@DTDTPA-Gd) were injected intravenously into mice, allowing for accurate tumor location to be displayed via MRI. This technique can be beneficial for targeted radiotherapy. Studies have shown that it significantly extends the lifespan of tumor-bearing rats.⁸⁰

Previous studies have demonstrated that Ag NPs possess a strong radio-sensitization ability when used in the treatment of U251 glioma cells.⁸¹ The mechanism involves promoting the apoptosis of tumor cells and increasing the level of autophagy. By employing Ag NPs, the radiation resistance of tumor tissue in hypoxic environment can be successfully decreased.^{33,82} Xu et al tested Ag NPs at concentration of one-tenth of the half maximal inhibitory concentration to target tumor cell, and found that Ag NPs, with a size of 20 nm, could significantly enhance the radiosensitivity of U251 glioma cells to X-rays without causing any toxic effects. These results indicate that Ag NPs also have the potential to be used in the sensitization of radiotherapy in gliomas.⁸³

Magnetic iron oxide nanoparticles have also been used in the treatment of recurrent glioblastoma. Magnetic iron oxide nanoparticles were infused into glioblastomas by the neuro navigation technique, and the nanoparticles were then heated in an alternating magnetic field, producing thermal energy. In conjunction with stereotactic radiation techniques, the tumors were irradiated with a dose of 10 Gy per week. The results showed a significant extension in the overall survival of patients with recurrent glioblastoma.⁸⁴ During the operation of fourteen cases of glioblastoma, aminosilane-coated iron oxide nanoparticles were injected into the tumor cavity under the guidance of 3D imaging technology, and then all patients received a single radiotherapy. The results showed that all patients had good tolerance to magnetic nanoparticles without any side effects. Using magnetic iron oxide nanoparticles for intracranial radiotherapy can further improve the sensitivity of radiotherapy.⁸⁵ In addition, Grauer et al coated two layers of superparamagnetic iron oxide nanoparticles on the wall of the tumor cavity after resection of the tumor in recurrent glioblastoma patients. Supplemented with heat and radiation therapy, there was persistent necrosis near the tumor tissue in the nanoparticle aggregation area. Immunohistochemistry showed that the number of macrophages was increased, the expression of caspase-3 and heat shock protein 70 was up-regulated. Intratumoral hyperthermia combined with radiotherapy could cause obvious inflammatory responses around the tumor, which further stimulated the anti-tumor immune response.⁸⁶ Overall, magnetic iron oxide nanoparticles play a significant role in enhancing immunoinflammation in the treatment of recurrent glioblastoma.

Photothermal Therapy

Photothermal therapy is a treatment method that utilizes materials with high optical energy conversion efficiency, combined with targeted recognition technology, to accumulate drugs near tumor tissues. Optical energy is converted into heat energy to kill cancer cells under certain conditions. Metal nanomaterials have emerged as excellent carriers for photothermal therapy, thanks to their distinctive optical properties, superior biological inertness, and local surface plasmon resonance (LSPR). Numerous metal materials, including gold and silver nanoparticles, generate a certain amount of heat upon light exposure, effectively killing tumor cells. Therefore, photothermal therapy is often combined with radiotherapy, chemotherapy, and surgery to improve anti-tumor effects.⁸⁷ Ordinary gold nanoparticles possess

a weak absorption capacity within the tissue penetrating NIR window, leading to the low efficiency of photothermal therapy. Wang et al discovered that fiber nanostructures assembled from positively charged spherical gold nanoparticles and negatively charged silk fibroin can improve the photothermal effect within the NIR window.⁸⁸ They synthesized spiropyrans and imidazole polymer-functionalized nanoparticles by surface polymerization technology. Photo-responsive polymer gold nanoparticles were obtained by reducing gold ions to the surface of the nanoparticles. The surface of the gold nanoparticles can also be modified with biotin to specifically target brain tumor cells. The nanoparticles showed potential benefits for enhancing photothermal and photodynamic therapies. In addition, they can be combined with certain specific antibodies to create functional nanoprobes.⁸⁹

Another metal nanomaterial, iron oxide, can also be used as thermos-sensitive nanoparticles for the treatment of tumors.⁴⁷ Lu et al used $\text{Fe}_3\text{O}_4@\text{Au}$ magnetic nanoparticles as the core shell, loaded with cetuximab to target glioma cells for photothermal therapy (Figure 4). These multifunctional nanomaterials can induce local plasma heating under the irradiation of NIR, which are less affected by the biological metabolism of tissues and cells. Moreover, metal oxide nanoparticles can also be utilized as photosensitizers in tumor photodynamic therapy. For example, the functionalized TiO_2 nanoparticles can be used in photodynamic therapy, and it is non-toxic and harmless in the absence of light irradiation and has a long blood circulation time in the body. However, using ultraviolet or visible light to directly irradiate tissues to trigger TiO_2 nanoparticles have some limitations. The tissue penetration depth of the light source at this wavelength is limited, and most tumor cells cannot be accurately targeted.⁹⁰ NIR, with the wavelength of 700 nm to 1000 nm, possesses the ability to infiltrate tumor tissues, thereby enhancing the efficacy of photodynamic therapy. Shigeru et al synthesized TiO_2 -PEG nanoparticles by adsorbing PEG onto the surface of TiO_2 . The TiO_2 -PEG showed significantly inhibition effects on the growth of glioma cells.⁸⁶ Photodynamic therapy using metal nanomaterials has increasingly emerged as a novel approach for the treatment of gliomas.

Metal Nanoparticles for Enhancing Biocompatibility and Reducing Toxicity

The toxicity of metal nanoparticles in glioma cells has gained significant attention due to their potential in targeted cancer therapies, where they can selectively deliver drugs or therapeutic agents directly to tumor sites. However, concerns about

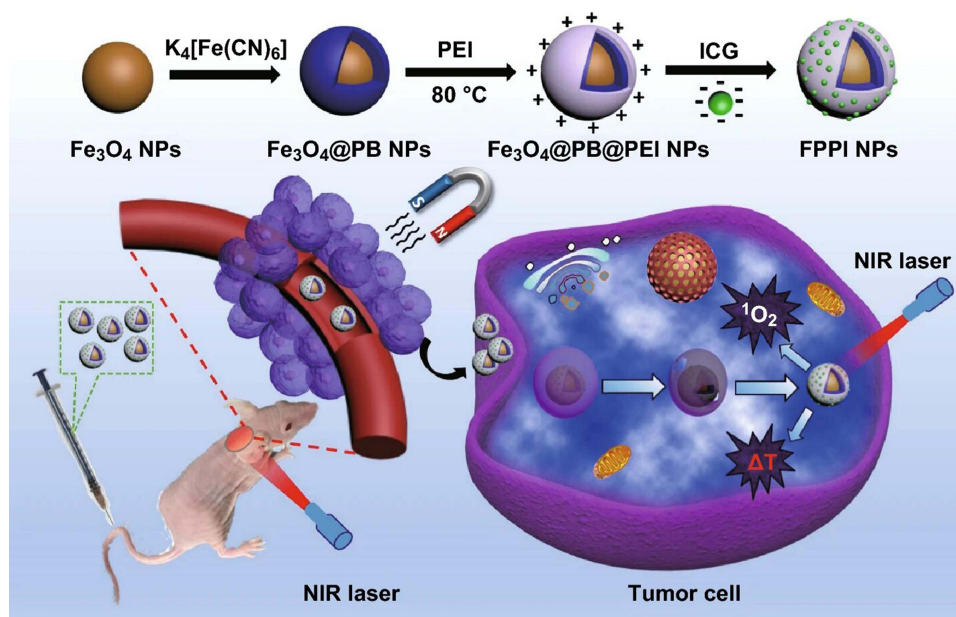


Figure 4 Magnetic oxide nanoparticles accumulate in the tumor region under the action of a magnetic field, generating hyperthermia and toxic ROS when exposed to NIR laser, and thereby killing tumor cells.

Note: Reprinted from Xue P, Yang R, Sun L, et al. Indocyanine Green-Conjugated Magnetic Prussian Blue Nanoparticles for Synchronous Photothermal/Photodynamic Tumor Therapy. *Nanomicro Lett.* 2018;10(4):74.⁴⁷

their biocompatibility, long-term stability, and potential bioaccumulation in healthy tissues persist, raising important questions about the balance between therapeutic efficacy and safety.⁹¹ A deeper understanding of the mechanisms behind nanoparticle toxicity in glioma is essential for developing safer, more effective treatments that minimize adverse effects on normal cells and organs.

To reduce the toxicity of metal nanoparticles in glioma therapy, several solutions have been proposed. First, surface modification techniques are key to minimizing toxicity. By coating the nanoparticles with biocompatible materials such as PEG or chitosan, their stability can be improved, and interactions with normal cells can be reduced, thereby minimizing damage to healthy tissues.^{92,93} Second, controlling the size and morphology of the nanoparticles is an effective approach. Smaller nanoparticles can more easily penetrate the BBB, but excessively small particles may cause higher cytotoxicity.⁹⁴ Therefore, optimizing the size and shape of the nanoparticles is crucial to balance therapeutic efficacy and safety.⁹⁵ In addition, the development of targeted delivery systems allows metal nanoparticles to specifically target glioma cells, reducing the impact on surrounding normal tissues.⁹⁶ Finally, adjusting the dosage and delivery timing can further minimize toxicity while enhancing therapeutic effects. The combination of these strategies provides a safer outlook for the clinical application of metal nanoparticles in glioma therapy.

Conclusions and Future Research

New treatment paradigms are urgently needed as the 5-year survival rate of GBM patients is still low. Recent advancements in nanomaterials have brought huge progress in the field of biology and medicine. In this paper, we summarized the properties of different types of metal nanomaterials, highlighting their advantages in the treatment and detection of gliomas. More importantly, we reviewed the potential applications of metal nanoparticles in glioma imaging, radiotherapy, chemotherapy, and photothermal therapy. Thanks to the excellent properties of metal nanoparticles, such as good electrical properties, optical properties, and magnetism, noble metal nanoparticles, metal oxide nanoparticles and metal quantum dots have been used to load chemotherapy drugs (eg, DOX, EGFR antibody), sensitize radiotherapy, and improve the photothermal effects in the treatment of gliomas. As shown in Table 1, a number of clinical trials are currently assessing the effectiveness and safety of nanodrugs in cancer treatment, detection, and precise targeted therapy. However, metal nanoparticles have not yet been utilized in clinical settings for the detection or treatment of gliomas. Nano-drugs face multiple challenges in entering clinical treatment for tumors, including complex preparation, high cost, poor stability, and significant toxic side effects. Ongoing research continues to push the boundaries of what's possible, but translating these innovations into practical, safe, and effective therapies is a complex process.

To address current knowledge gaps in metal nanoparticle research, future studies should employ a range of methodologies. Longitudinal studies are crucial for assessing long-term effects, such as stability, toxicity, and tissue accumulation, while also helping to define safe dosage limits. In vivo models that closely replicate human physiology can provide valuable data on therapeutic efficacy and biocompatibility, highlighting interactions with biological systems and patterns of biodistribution. High-throughput screening can rapidly optimize nanoparticle formulations, refining key parameters like size, surface charge, and functionalization to maximize efficacy and minimize toxicity. Additionally, analyzing molecular pathways influenced by metal nanoparticles—such as those involved in inflammation and apoptosis—can help improve both design specificity and therapeutic outcomes. Advanced imaging techniques, such as real-time fluorescence imaging and MRI, can complement these efforts by enabling detailed tracking of biodistribution and cellular uptake. Together, these approaches offer a comprehensive framework for enhancing our understanding of metal nanoparticle behavior and guiding the safe, effective development of nanoparticle-based therapies in gliomas.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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