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Therapeutic Delivery

Recent advancements in brain tumor targeting using magnetic nanoparticles

Himanshu Gandhi[1], Abhishek Kumar Sharma[1], Shikha Mahant[1] & Deepak N Kapoor*,[1]
[1]School of Pharmaceutical Sciences, Shoolini University of Biotechnology & Management Sciences, Post box No. 9, Distt. Solan – 173212 (HP), India
*Author for correspondence: deepakpharmatech@gmail.com

Transport of drugs through the blood–brain barrier to the brain and the toxic effects of drugs on the healthy cells can limit the effectiveness of chemotherapeutic agents. In recent years, magnetic nanoparticles (MNPs) have received much attention as targeted therapeutic and diagnostic systems due to their simplicity, ease of preparation and ability to tailor their properties such as their composition, size, surface morphology, etc. for biomedical applications. MNPs are utilized in drug delivery, radio therapeutics, hyperthermia treatment, gene therapy, biotherapeutics and diagnostic imaging. The present review will address the challenges in brain tumor targeting and discuss the application and recent developments in brain tumor targeting using MNPs.

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Brain tumor or intracranial tumor is an abnormal mass of tissue that multiplies in an abnormal way in the brain and can directly destroy healthy cells of the brain. Brain tumors are the leading source of morbidity and mortality worldwide. The average incidence of brain cancer is 10.82 per 100,000 person-years [1]. According to data from the International Agency for Research on Cancer (IARC), 296,851 new cases and 241,037 deaths related to cancers of the brain and nervous system are projected to occur worldwide in 2018 [2]. In the USA, cancers of the brain and nervous system are the second most common cancer type in children and adolescents and the prime cause of cancer-associated death before 40 years of age [3].

Brains tumors are generally divided into glioma and nonglioma tumors [4]. Gliomas are the most common type of primary brain tumor in adults. Gliomas originate from supportive cells in the brain called glial cells, which include astrocytomas, oligodendrogliomas and ependymomas. Astrocytomas are derived from the star-shaped glial cells (astrocytes) which surround and protect neurons. Astrocytomas account for approximately 70% of primary brain tumors and occur most often in the cerebrum [5]. Low-grade astrocytoma (grade I or grade III) are often benign (noncancerous) and rarely spread to nearby tissues whereas, anaplastic astrocytoma (grade III) and grade IV astrocytoma, tumor cells multiply and can spread throughout the brain. Oligodendroglioma develops from oligodendrocytes, which are the cells responsible for making myelin in the brain and account for 9% of primary CNS tumors in adults and 4% of primary CNS tumors in children [6,7]. Ependymomas originates in the ependymal cells that line the passageways and ventricles in the spinal cord and brain where cerebrospinal fluid (CSF) flows. Ependymomas occur most often in children and account for 8–10% of primary CNS tumors in children [5]. Nonglioma tumors include meningioma, pituitary gland tumors, primary CNS lymphoma, medulloblastoma, schwannoma and craniopharyngioma [4]. Meningiomas grow from the meninges and constitute 35% of all primary brain tumors. Meningiomas are generally benign and are most often noncancerous. Meningioma grows slowly and can cause severe symptoms as they can suppress and damage brain tissue or spinal cord. Primary CNS lymphoma do not spread systemically and are limited to brain spinal fluid and eye [8]. Medulloblastomas originate in cerebellum and account for 2% of all types of cancers in children [9]. Vestibular Schwannoma, a benign vestibular nerve sheath tumor, also known as acoustic neuroma, develops due to slow and excessive generation of schwannoma cells [10]. Craniopharyngiomas, commonly found in adolescents and children, are benign tumors that form near

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pituitary gland and constitute less than 1% of all brain tumors. These can severely disturb the functioning of hypothalamus [4,11].

Despite advances in the treatment of brain tumors, the prognosis for patients with a high-grade malignant brain tumor is low [12,13]. Therapeutic approaches for brain metastases include medical procedures, entire brain radiation treatment, stereotactic radiosurgery, chemotherapy, development factor inhibitors or a mix of these treatments [14]. Brain tumors can be treated by chemotherapy that involves the use of cytotoxic and cytostatic agents that are administered at different time points [15]. The mechanism of these therapies includes direct tumor cell death, anti-angiogenesis development factor pathway disturbance and hindrance of tumor attack. Temozolomide (TMZ), an imidazotetrazine derivative, has shown great potential in treating patients with malignant gliomas and other difficult to treat tumors [16,17].

Advanced functional imaging methods for brain tumor imaging assume a basic part in administration as it takes into consideration early detection, careful arranging and follow-up assessment. Imaging methods for brain tumors include magnetic resonance imaging (MRI) [18], computed tomography [19] and positron emission tomography [20]. All these techniques along with other imaging methods such as fluorescence guided tumor resection are well established techniques for intraoperative imaging. These advanced imaging techniques can help doctors make the proper diagnosis and help them choose the most appropriate treatment [17,21]. Management of brain tumors and their problems requires complex coordination of care between primary care providers, restorative oncologists, radiation oncologists and neurosurgeons. Despite availability of a number of sophisticated diagnostic techniques and therapeutic options, brain tumor treatment is still a challenge for oncologists [22]. Some of the major challenges for the successful treatment of brain tumors are the highly invasive and complex structure of the human brain, inadequate accumulation of therapeutic agents at the tumor site and acquired drug resistance to cancer, these limitations may reduce the overall effectiveness of the treatment.

Various physiological barriers that hinder the efficiency of systemic delivery of therapeutic agents to brain tumors are the blood–brain barrier (BBB), the blood–CSF barrier (B-CSF), and the blood–brain tumor barrier (BBTB). Unlike other organs, the brain is protected by the BBB. This protective BBB is essential for correct neuronal functioning of the brain and manages the ionic composition for appropriate synaptic flagging function. It also protects the CNS from neurotoxic substances and prevents the entry of macromolecules and undesirable cells into the brain [22,23].

Endothelial cells of the BBB along with astrocytes, pericytes and perivascular macrophages together constitute the neurovascular unit [24]. Astrocytes maintain the barrier function of the endothelium and pericytes maintain the structure of the BBB [25,26]. Further, multidrug-resistant proteins such as P-glycoproteins are drug efflux transporters that control drug movement across the BBB [27]. Lipophilic drugs with particle size in the range of 400 to 600 Da can only penetrate through the BBB into the brain [24]. The B-CSF is comprised of tightly bound choroid epithelial cells that restrict particle penetration inside the interstitial fluid of the brain parenchyma [28]. They can actively expel therapeutic organic acids from the B-CSF and, as a result, avoid their diffusion into the brain parenchyma [29,30]. The BBTB in the tumor is predominantly framed by brain tumor capillaries, and it is the third barrier for transporting therapeutic agents [31]. The leaky tumor vasculature creates high intra-tumoral interstitial pressure that limits the penetration of the therapeutic agent from the systemic circulation into the tumor. Additionally, the structure–function properties of different tumor micro-vessel populations can significantly compromise therapeutic results [31,32]. In low-grade gliomas, the typical vascularization and the function of the BBTB remain intact for the most part and resemble BBB. Variations in the vascular function and leaky BBTB are specific indications of high-grade gliomas [23]. Various anticancer agents have been reported to be effective against the treatment of brain tumors. TMZ is the first-line drug for the treatment of high-grade brain tumors, especially anaplastic astrocytoma and glioblastoma [17]. Other drugs include carmustine, lomustine, procarbazine, cisplatin and vincristine. However, clinical failure was observed due to the inadequate transport of such drugs across the barrier. These significant drawbacks are observed either due to the hydrophilic nature of the molecules or due to high molecular weight. Currently, US FDA-approved anticancer agents employed for the treatment of brain tumors are enlisted in Table 1 [33]. Magnetic nanoparticles (MNPs) are an important class of nanomaterials that have the potential to transform current clinical diagnostic and therapeutic techniques. Recently, MNPs have gained significant attention because of their tremendous potential as contrast agents for MRI and as a heating mediator in hyperthermia therapy [34].

Table 1. List of drugs approved by the US FDA for the treatment of brain tumors.

Name of drug	Manufacturer	Dosage form	Targeting efficacy (%)	Adverse effect
Temozolomide	Accord Healthcare Inc., Cadila Healthcare Limited, Amerigen Pharmaceuticals Inc., Sandoz Inc., Teva Pharmaceuticals, Merck Sharp & Dohme Corp., Sun Pharmaceutical Industries	Capsule, injection, powder, lyophilized, solution	0.63†	Thrombocytopenia, myelosuppression, nausea, vomiting, anorexia and constipation
Everolimus	Novartis Pharmaceuticals Corporation	Tablets, tablets for suspension	35‡	Noninfectious pneumonitis, severe hypersensitivity reactions, stomatitis, renal failure, impaired wound healing, metabolic disorders myelosuppression
Bevacizumab	Genentech Inc, Amgen Inc	Injection	0.91§	Gastrointestinal perforations and fistulae, hemorrhage, venous thromboembolic event, hypertension, injury and proteinuria, congestive heart failure
Carmustine	Heritage Pharmaceuticals, Inc.	Injection	0.73¶	Myelosuppression, pulmonary toxicity, administration reactions, carcinogenicity ocular toxicity
Carmustine Implant	Arbor Pharmaceuticals	Implant	6.15#	Seizures, intracranial hypertension, impaired neurosurgical wound healing, meningitis
Lomustine	H3 Medical In, AX Pharmaceutical Corp, NextSource Biotechnology LLC	Powder, capsule gelatin coated	13.9††	Delayed myelosuppression, risks of overdosage, pulmonary toxicity, secondary malignancies, hepatotoxicity

†The hazard ratio for overall survival from newly diagnosed glioblastoma multiforme compared with radiotherapy alone.
‡The main efficacy outcome measure in terms of subependymal giant cell astrocytoma (SEGA) response rate as a reduction in the sum of SEGA volume relative to baseline according to the independent central radiology review.
§The main efficacy outcome measures in terms of hazard ratio for overall survival from recurrent glioblastoma.
¶Overall survival rate in terms of hazard ratio for newly diagnosed high-grade gliomas with comparison to placebo.
#Median overall survival for glioblastoma with gliadal wafers compared with placebo wafers.
††Objective response rate for glioblastoma with lomustine compared with lomustine plus bevacizumab.

Magnetic nanoparticles

Nano-based drug-delivery systems such as liposomes, lipid/polymeric nanoparticles (NPs), MNPs, niosomes and dendrimers can encapsulate various therapeutic agents such as small and hydrophilic molecules. MNPs such as iron oxide NPs (IONPs), superparamagnetic iron oxide NPs (SPIONs) and fluorescent MNPs are widely used as diagnostic imaging agents and therapeutic delivery vehicles. Recent advancements in nanotechnology have led to the possibility to tailor the properties of MNPs such as their composition, size, surface morphology, etc. for biomedical applications [35]. Figure 1 shows the diagrammatic representation of multifunctional MNPs. Some of the well-known techniques that have been used for the synthesis of MNPs are microemulsion, chemical vapor deposition, sonochemical, solvothermal, co-precipitation, microwave-assisted, thermal decomposition, combustion, carbon curve and laser pyrolysis synthesis [36]. MNPs consist of an inorganic iron oxide core and a biocompatible surface coating that is suitable for physiological conditions [37]. MNPs can play numerous functions at the same time, including multimodal imaging [38], drug delivery, real-time monitoring and combined therapeutic methodologies.

Applications of MNPs conjugated with specific ligands is one of the key techniques that have been explored for active targeting of the chemotherapeutic agents at the tumor site. Drug targeting to the required site by using the magnetic delivery system is based on the force exerted by the particles and magnetic force generated by the external magnet [36].

Figure 2 shows the mechanism for brain targeting by MNPs. After intravenous administration, MNPs are exposed to the external magnetic field by positioning the rat head close to the magnet, which increases the movement of magnetic particles in the systemic circulation toward the brain [27]. The ligand attached to the surface of the magnetic particle can help the particles to cross the BBB by attaching to the receptors present on the BBB for the particular ligand. These magnetic particles then cross the blood–tumor barrier by attaching to the receptor expressed for the ligand attached to the magnetic particles. At last, MRI images of the rat brain exposed to the magnetic field are taken which shows the accumulation of NPs in the brain tumor.

The main limitation of drug delivery through MNPs is related to the external magnetic field strength that can be applied to obtain the required magnetic gradient necessary to control the residence time of MNPs in the target region. The small size of NPs implies a magnetic response of low strength, thus making it challenging to direct particles and to control their residence time in the proximity of the target. Targeting is likely to be more productive

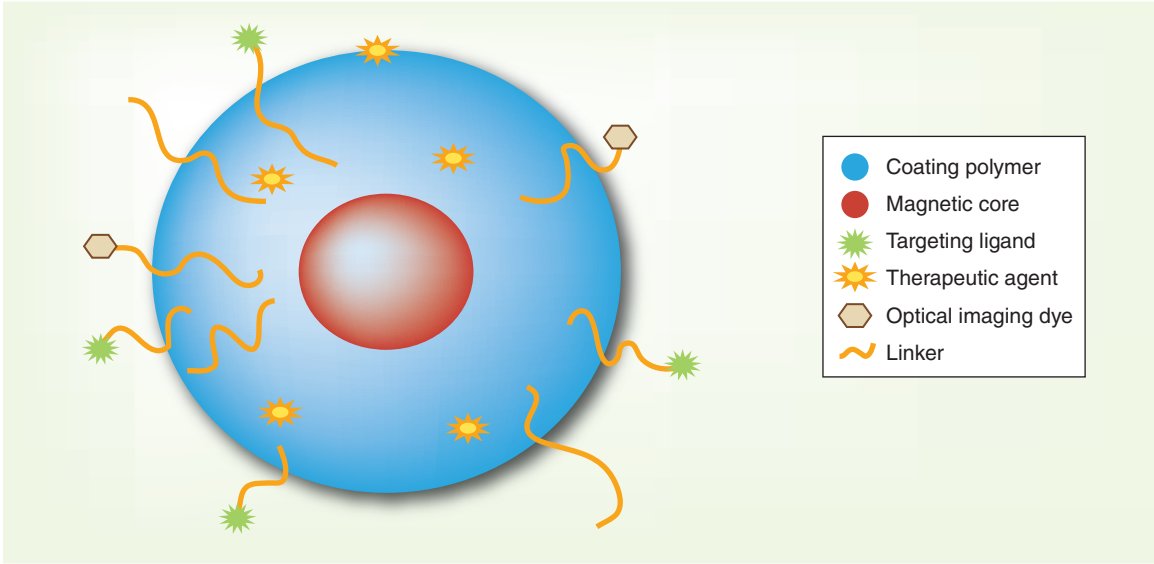

Figure 1. Core–shell structure of magnetic nanoparticle and multifunctional surface.

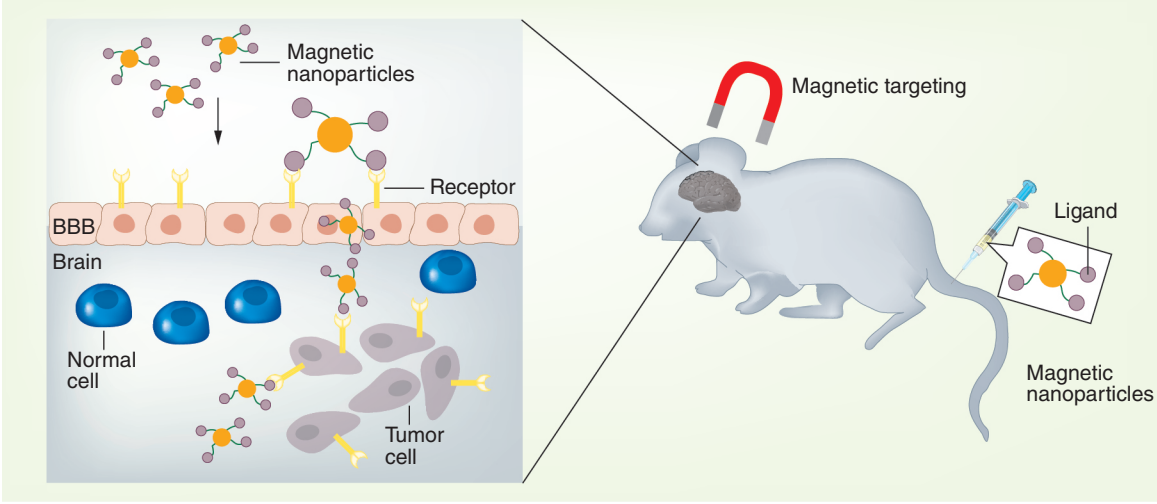

Figure 2. Magnetic nanoparticles as a vehicle in brain tumor targeting and its mechanistic approach for brain tumor targeting.

when the source of the magnetic field is close to the target region and in areas where the velocity of the blood flow is low [39].

MNPs for diagnosis & treatment of tumor

MNPs have been widely used for diagnosis and treatment of brain cancer. Some of the modified MNPs reported for brain targeting are shown in Table 2. Ling and colleagues synthesized a multifunctional nanotheragnostic system by coating TMZ-loaded PLGA-based SPIONs with polysorbate 80 [40]. This developed system exhibited excellent sustained release of drug TMZ for 15 days. MTT assay and fluorescence microscopy studies showed significant cellular uptake of the multifunctional nano-theragnostic system. Furthermore, MRI scanning confirmed the enormous potential of the prepared NPs as an MRI contrast agent. The anticancer efficacy of binding tumor growth-inhibiting synthetic peptides to hydrothermally synthesized magnetoelectric NPs (MENs) was investigated by Stewart *et al.* [41]. The study confirmed the binding of the MIA class (MIA-690) to MENs with high efficacy and their targeted specificity to glioblastoma cells. Furthermore, the on-demand release of the peptide by the application

Table 2. Magnetic nanoparticles for brain targeting.

Drug	Delivery system	Animal model studied	Route of administration	Size (nm)	Ref.
Temozolomide	PLGA-based super-paramagnetic nanoparticles	-	-	197–220	[40]
BCNU	Magnetic nanoparticles	Rat brain tumor model	External jugular vein	89.2 ± 8.2	[42]
Paclitaxel	Magnetic nanoparticles	Rat model	Intravenous through the saphenous vein	~150–200	[43]
Doxorubicin and Paclitaxel	Transferrin-conjugated magnetic silica PLGA nanoparticles	Male BALB/c nude mice	External jugular vein	~150	[44]
-	Magnetic iron oxide nanoparticles	Male Fisher 344 rats	Intravenous or intra-arterial route	110 ± 22	[45]
-	Magnetic PAEEP-PLLA nanoparticles with lactoferrin (LF)	Rat model	Tail vein	218.2 ± 0.4	[46]
-	Magnetic iron oxide nanoparticles	Male Fisher 344 rats	Intravenous	100	[27]
-	Iron oxide nanoparticles	Male Fisher 344 rats	Nanoparticle suspension through the catheter	110 ± 22	[12]
	LF-conjugated super-paramagnetic iron oxide nanoparticles	Rat model	Tail vein	74.8 ± 11.5	[47]
-	VEGF-targeted magnetic nanoparticles	Wistar rats	Intravenous	90 ± 2–97 ± 3	[48]
	PEG-modified, cross-linked starch-coated iron oxide nanoparticles	male Fisher rats	Tail vein	134.3 ± 2.1	[13]
	Polyethyleneimine-modified iron-oxidenanoparticles	male Fisher 344 rats	Intracarotid	225	[49]
	Folate conjugated fluorescent magnetic albuminnanoparticles	-	-	15-20	[50]
Chlorotoxin	Dual-target conjugated on iron oxide nanoparticles	Mouse model	Intravenous	~90–200	[51]
Paclitaxel and Curcumin	Dual-Targeting magnetic PLGA nanoparticles	Mouse model	Tail vein injection	130	[52]
Curcumin	Curcumin Dual-targeting LF-conjugated polymerized magnetic polydiacetylene assembled nanocarriers	Rat	Intravenous	100–120	[53]
Cetuximab	Convection-enhanced delivery of cetuximab conjugated iron-oxide nanoparticles	Intracranial gliomas model in canines	Intravenous catheter	100	[54]
Paclitaxel	Magnetic targeting of paclitaxel-loaded PLGA based nanoparticles	Nude mice	Tail vein	250 ± 20	[55]
-	EGF1 derived from coagulation factor VII functionalized iron oxide nanoparticles	BALB/c nude mice	Right striatum region with a microinjector	42.8 ± 8.5 – 44.5 ± 8.6	[56]
-	Monoclonal antibody-conjugated superparamagnetic iron oxide	Wistar rat model	Intracarotid	161.5 ± 2.12	[57]
Temozolomide	Superparamagnetic iron oxide nanoparticle polymeric nanocomposite	NOD-SCID mice	Tail vein	84.37 ± 12.37 – 101.56 ± 7.42	[58]
-	Superparamagnetic iron oxide coated nanoparticles with gold (SPIO@Au) and labeled with mesenchymal stem cells	Mouse model	Carotid artery	82	[59]
Doxorubicin	Superparamagnetic iron oxide nanoparticles with PEGylated phospholipid coating	BALB/c nude mice and Wistar rats	Tail vein	22.9	[60]
Cisplatin	Magnetic nanoparticles conjugated with lactoferrin (LF) and RGD dimer	Mouse model	-	9.8 & 4.7	[61]
-	Chitosan-based superparamagnetic iron oxide nanoparticles	Male Wistar rats	Intravenous	55	[62]
-	Magnetic nanoparticle Hsp70 conjugate	Male Wistar rats	Intravenous	35	[63]
-	Superparamagnetic iron oxide nanoparticles conjugated with epidermal growth factor (SPION–EGF)	Male Wistar rats	Intravenous	47.6	[64]
-	Interleukin-1 receptor antagonist conjugated to superparamagnetic iron oxide nanoparticles	Male Wistar rats	Intravenous	43.1	[65]
-	Superparamagnetic iron oxide nanoparticles conjugated with cmHsp70.1 monoclonal antibodies	Male Wistar rats	Intravenous	42.7 ± 2.3	[66]
O^6-Benzylguanine and Temozolomide	Redox-responsive magnetic nanoparticle	Mouse model	Tail vein	76	[67]

BCNU: 1,3-Bis(2-chloroethyl)-1-nitrosourea; PEG: Poly (ethylene glycol); PAEEP-PLLA: Poly(aminoethyl ethylene phosphate)/poly(L-lactide); PLGA: Poly(lactide-co-glycolide).

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Table 2. Magnetic nanoparticles for brain targeting (cont.).

Drug	Delivery system	Animal model studied	Route of administration	Size (nm)	Ref.
-	Magnetoelectric nanoparticles (MEN)	-	-	30	[41]
-	Fe_3O_4 magnetic nanoparticles functionalized with folic acid and gH625 peptides	-	-	109 ± 4 & 52 ± 6	[68]
-	Polyethyleneimine (PEI)-coated Fe_3O_4 nanoparticles for the therapeutic delivery ofsiRNA.	-	-	18.21	[69]
Cetuximab	Iron-oxide nanoparticles	Nude female mice	-	19	[70]

BCNU: 1,3-Bis(2-chloroethyl)-1-nitrosourea; PEG: Poly (ethylene glycol); PAEEP-PLLA: Poly(aminoethyl ethylene phosphate)/poly(L-lactide); PLGA: Poly(lactide-co-glycolide).

of the magnetic field was also possible. These results provide an excellent example of the enormous potential of MENs as an efficient drug-delivery system for growth hormone-releasing hormone antagonists for the glioblastoma treatment.

The potential efficacy and safety of IONPs conjugated with cetuximab (CET; IONPs-CET) for the treatment of intracranial gliomas in canines after convection-enhanced delivery (CED) were evaluated by Freeman *et al.* [54]. The direct infusion of CET-IONPs by peritumoral and intra-tumoral route was also possible by the use of CED, which could avoid the BBB and limit systemic effects. A single CED treatment of IONPs-CET was given to eight dogs for 3 days, and MRI studies confirmed a median reduction of 54.9% in tumor size. Shevtsov and coworkers prepared hybrid chitosan-dextran SPIONs through ionotropic gelation in the superparamagnetic state [62]. Hybrid CS-DX-SPIONs were found to have a tumor-targeting potential and high MRI contrast-enhancing activity. *In vitro* studies confirmed that the coating of the NPs by chitosan enhanced the intracellular uptake of particles and consequently increased their cytotoxic action. In another study, Wang *et al.* developed polyethyleneimine-coated Fe_3O_4 NPs and utilized them as a vehicle for siRNA delivery into glioblastomas for silencing of repressor element 1-silencing transcription factor (REST) [69]. Western blotting and real-time polymerase chain reaction studies showed a significant reduction of REST in translation and transcription levels. Furthermore, targeting of REST by NP/siRNA inhibited the viability of glioblastomas and repressed their migration capacity.

Fenton reaction accelerable MNPs, in other words, cisplatin-loaded Fe3O4/Gd2O3 hybrids conjugated with lactoferrin (LF) and RGD dimer (FeGd-HN@Pt@LF/RGD2), were explored by Shen *et al.* for ferroptosis therapy of orthotopic tumors in the brain [61]. Results revealed that the efficiency of ferroptosis therapy was considerably improved by accelerating the Fenton reaction. It resulted in the production of reactive oxygen species, which led to significant cancer cell death. Moreover, the intrinsic MRI capability of these NPs can be used to examine the tumor response to ferroptosis therapy. To enhance targeting specificity to gliomas in the brain and improve the MR contrast effect, Ai *et al.* prepared dual targeting Fe3O4 NPs of different relative lengths with PEGylated folic acid (PEG-FA)/chlorotoxin (CTX) and further labeled them with cyanine 5.5 (Cy5.5) [51]. It was observed that by adjusting the relative length of the dual target, the targeting of prepared NPs to the brain glioma could be modulated.

In order to target $\alpha_v\beta_3$ overexpressed integrin in brain tumors, a new nanosystem was synthesized by Richard *et al.* [71]. IONPs were functionalized with phosphonate poly(ethylene glycol) POPEG-COOH to improve the stability of NPs in the biological media. Under microwave conditions, the carboxylate end functions were further grafted with cRGD peptide. It was observed that the active targeting induced by cRGD peptides onto the surface of NPs resulted in the accumulation of the prepared nanoplatforms in tumor tissue 1 day after injection. Another study reported the development of SPION polymeric nanocomposite containing TMZ [58]. In order to cross the BBB and target the tumor, nanocomposites were coated with transferrin/polysorbate 80 and tagged with an antibody against nestin, a stem cell marker. The researchers found that the sustained release of TMZ from the nanocomposite led to a significant reduction in tumor volume in comparison with the pure TMZ. SPIONs based multimodal theragnostic nanoplatforms containing antitumor drug doxorubicin (DOX) and fluorescent dye Rhodamine B isothiocyanate for theragnostic analysis were developed by Wang *et al.* [50] The nanoplatform was further conjugated with tumor-specific ligand Tf and was delivered into U251 MG glioblastoma cell lines to access its biological effects. The results indicated that the nanoplatform could efficiently inhibit the proliferation of cells and induce apoptosis in the treated U251 MG glioblastoma cells.

Glioblastomas could be recurrent and one of the reasons could be their invasive nature and indistinct tumor margins. EGF1 was conjugated with iron oxide NPs by Lin *et al.*, for the precise delineation and detection of gliomas

in the brain [72]. The synthesized EGF1-EGFP-IONPs demonstrated excellent targeting capability toward human umbilical vein endothelial cells and tissue factor (TF)-positive U87MG cells *in vitro*. Moreover, the prepared NPs efficiently enhanced MR contrast for up to 12 h in preclinical glioma models. The antioxidative properties of IONPs functionalized with caffeic acid were explored by Richard *et al.* on *in vitro* U87-MG brain cancer cell lines [73]. Cell proliferation assays confirmed the antioxidant effect of the NPs. Negative contrast enhancement was also observed after intravenous injection of NPs in mice bearing. Fang and group developed new LF-modified dual targeting magnetic polydiacetylene nanocarriers delivery system encapsulating curcumin [53]. Data from animal studies indicated that controlled release and LF-targeting synergistically suppressed tumors in orthotopic brain bearing rats and improved the retention time of the encapsulated curcumin. A magnetic PLGA NP system modified by T7 peptide was prepared by Cui *et al.* by co-encapsulating drugs (curcumin and PTX) and hydrophobic MNPs [52]. Dual targeting improved the cellular uptake and brain delivery in mice bearing orthotopic glioma as compared with the nontargeting NPs. Furthermore, the system reduced the adverse effects and showed enhanced treatment efficiency in mice.

Recently, magneto fluorescent NPs have gained significant research interests among the scientific community due to their potential applications in imaging and biological manipulation. Demillo & Zhu prepared zwitterionic magneto fluorescent NPs (ZW-MFNPs) in the form of micelles [74]. The hydrophobic cores of the ZW-MFNPs were further integrated with CuInS2/ZnS quantum dots, and $MnFe_2O_4$ MNPs and their hydrophilic shells were integrated with zwitterionic groups such as sulfobetaine and carboxybetaine. ZW-MFNPs showed excellent imaging properties, negligible cytotoxicity and specifically targeted tumor cells in the brain after conjugation with chlorotoxin. Boucher *et al.* synthesized genetically engineered magnetosomes and explored their potential as a new MRI probe [75]. The magnetosomes were later functionalized with an RGD peptide. *In vivo* studies confirmed the accumulation of the functionalized magnetosomes at the tumor site after tail vein injection in glioblastoma-bearing mice. Moreover, enhancement of tumor contrast was observed on MR images.

The EGFR represents a primary therapeutic target as it is commonly overexpressed in malignant glioma. SPIONs conjugated to recombinant human EGF (SPION–EGF) were fabricated by Stevtsov *et al.* [64]. The SPION–EGF conjugates were later used as an agent for MRI contrast enhancement of EGFR-overexpressing C6 gliomas. The conjugates showed no toxic effects and high intracellular incorporation was observed on C6 cell proliferation and viability. Administration of the prepared SPION–EGF conjugates by intravenous route provided targeted delivery across the BBB in animals. Glioblastoma stem-like cells (GSCs), which are commonly found in tumors, are responsible for tumor recurrence and are tumorigenic in nature. Multifunctional IONPs conjugated with CET, an EGFR inhibitor, were synthesized by Kaluzova *et al.* [70]. They later determined their targeting effects with EGFR and EGFRvIII-expressing GSCs and neurospheres. The prepared CET-IONPs were found to have a significant antitumor effect compared with CET alone due to EGFR internalization, EGFR signalling alterations and induction of apoptosis in EGFR-expressing GSCs and human glioblastoma neurospheres. Shevtsov *et al.* developed SPIONs conjugated with Hsp70, which binds selectively to CD40 receptor present in glioma cells [63]. Further study revealed that SPION-Hsp70 conjugate accumulated in tumors and enhanced MR contrast after intravenous administration in a C6 glioma model. In another study, Shevtsov *et al.* evaluated the anti-edema effect and the possible application of SPIONs conjugated with interleukin-1 receptor antagonist (IL-1Ra) as negative magnetic resonance contrast agents [66]. Results suggested that intravenous administration of SPION–IL-1Ra in rats with intracranial C6 glioma considerably reduced the peritumoral edema and prolonged the life span of animals in contrast with the control group. Moreover, the synthesized SPION–IL-1Ra conjugates exhibited the properties of a negative contrast agent suggesting their great potential application in theranostic approach for the diagnosis of brain tumors.

Mu and group synthesized SPIONs conjugated with EGFRmAb and analyzed their potential role as an MRI contrast agent for EGFR specific detection of gliomas in the brain [57]. The *in vivo* examination in rats bearing C6 glioma and *in vivo* studies in C6 cells confirmed the accumulation of EGFRmAb-SPIONs within glioma and their possible role as an MRI contrast agent. Moreover, based on the laboratory examinations, EGFRmAb-SPIONs showed no *in vitro* and *in vivo* toxicity. A magnetic NP-based platform through cationic polymer modification was utilized by Wu *et al.* to promote radiotherapy for the treatment of glioma [76]. It was observed that the MNP-based platform induced cytotoxicity to glioma cells under the influence of radiation and manipulated the myeloid phenotypes in the CNS. Shen *et al.* developed a multifunctional nano-theragnostic agent by simultaneously loading DOX and indocyanine green into the SPIONs.

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The SPIONs were later coated with PEGylated phospholipid for magnetic resonance and treatment of glioma [60]. The NPs possessed excellent imaging capacities and were able to penetrate through the BBB. Furthermore, these NPs enhanced the cytotoxicity effects against glioma cells in comparison to free DOX administration in rats and showed a lesser number of side effects. A versatile route based on magnetic Fe_3O_4 NPs prefunctionalization with phosphonic acid monolayer was explored by Tudisco *et al.* for covalently binding a membranotropic peptide (gH625) onto the surface of the NPs [68]. The study concluded that the functionalization of MNPs with gH625 improved the internalization of NPs into the endothelial cells, suggesting a potential strategy in designing functional nanostructures with the ability to cross the BBB and reach tumor site in the brain.

Quia *et al.* reported the synthesis of SPIONs coated with gold (SPIO@Au) and evaluated their feasibility in visualizing bone marrow-derived human mesenchymal stem cells (MSCs) [59]. MSCs were conjugated with a green fluorescent protein and labeled with SPIO@Au. These NPs were then injected into glioma bearing mice via the carotid artery. The results revealed that MSCs labeled by SPIO@Au exhibited no cell death or any adverse effects on migration and differentiation. Furthermore, it also enhanced their photoacoustic imaging in contrast with tumors that were injected with unlabeled MSCs. Antitumor efficacies and targeting strategies of paclitaxel (PTX) and SPIO-loaded PLGA-NPs were explored by Ganipineni *et al.* [55]. The PTX and SPIO-loaded PLGA-NPs showed a concentration-dependent cellular uptake. Magnetic targeting resulted in the accumulation of NPs in the brain and also enhanced the antitumor efficacy in comparison with the saline treatments and passive targeting. Dilnawaz *et al.* developed PTX-loaded MNPs (Pac-MNPs) conjugated with glycoprotein nonmetastatic melanoma protein B (GPNMB) for active targeting because GPNMB is overexpressed in brain tumor cells [43]. MNPs showed excellent contrasting properties, as demonstrated by *in vivo* liver and brain images of the rat. In addition, the therapeutic efficacy of PTX-MNPs in glioma cell lines revealed that it could be an effective theranostic system for brain tumor treatment.

Hua *et al.* prepared three different types of MNPs, in other words, MNP-1, MNP-2 and MNP-3 by varying the concentration of polymer poly-[aniline-co-N-(1-one-butyric acid) aniline] (SPAnH) used for coating of iron oxide (Fe_3O_4) cores [42]. These MNPs were developed to improve the therapeutic efficacy and thermal stability of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). BCNU is an anticancer agent used for the treatment of brain tumors. They found that the maximum effective dose of BCNU was immobilized on MNP-3 (Bound-BCNU-3). Results also revealed that by using an external magnetic field *in vivo* and *in vitro*, the concentration of Bound-BCNU-3 increases at the target site. Thus, it could be a promising strategy for the transport of drugs across the BBB by using an external magnet. Transferrin (Tf) conjugated magnetic silica PLGA NPs loaded with drugs DOX and PTX were prepared by Cui *et al.* [44]. It was found that by using a magnetic field and targeting ligand Tf, cellular uptake and delivery of drug-loaded NPs can be enhanced. DOX-PTX-NPs-Tf exhibited superior *in vitro* cytotoxicity and *in vivo* therapeutic efficacy in comparison to those treated with DOX-PTX-NPs, PTX-NPs-Tf and DOX-NPs-Tf.

The factors affecting brain tumor targeting after carotid or intravenous administration of NPs under the influence of the magnetic field were investigated by Chertok *et al.* [45]. A 1.8-fold increase in NP concentration in brain tumor with an applied magnetic field of 350 mT was observed in comparison to NP accumulation with a magnetic field of 150 mT in the case of carotid administration. The results indicated that the carotid administration of NPs by applying a strong magnetic field at the tumor site will provide a more significant advantage in terms of tumor targeting. Luo *et al.* prepared Fe_3O_4 MNPs by thermal decomposition method and coated them with oleylamine (OAM) [46]. These NPs were then encapsulated into novel amphiphilic poly(aminoethyl ethylene phosphate)/poly(L-lactide) (PAEEP-PLLA) copolymer NPs. OAM-MNPs loaded PAEEP-PLLA NPs were also conjugated with LF ligand which is an effective ligand for brain tumor targeting. The vibrating sample magnetometer (VSM) results confirmed the superparamagnetic nature of OAM-MNPs and Lf-M-PAEEP-PLLA-NPs. Lf-M-PAEEP-PLLA-NPs exhibited good cytotoxicity, high cellular uptake in C6 glioma cells and also significantly enhanced the contrast images of MRI in Wistar rat bearing glioma.

Magnetic iron oxide NPs (MIONs), modified with free thiol (SH) conjugated with bifunctional polyethylene glycol (PEG) was developed by Lee *et al.* [27]. Exposure of the circulating MIONs-PEG-SH to an external applied magnetic field leads to the formation of disulphide bond by subsequent interaction between the MIONs and also increases the local concentration of MIONs-PEG-SH in brain tumor. The results indicated that the retention and accumulation of MIONs loaded with DOX in the rat brain tumor model could also be enhanced by applying an external magnetic field. IONPs conjugated with LF (LF-SPIONs) have been developed as an MRI contrasting agents for highly selective and sensitive detection of brain gliomas [47]. Over a period of 48 h, the Lf-SPIONs accumulated in glioma and also enhanced the contrast between the tumor and surrounding brain tissues. Lf-

SPIONs can be utilized in both preoperative and postoperative situations. Long circulating PEG modified starch cross-linked MNPs (PEG-MNPs) that are suitable for *in vivo* targeting have also been reported by Cole *et al.* [13]. The bio-distribution study of PEG-MNPs in the kidney, spleen, lung and liver of rats was also performed. The amount of PEG-MNPs in the liver was found to be lower than other MNPs, which could lower the NP related liver toxicity. However, higher concentration of PEG-MNPs was found in the spleen, which may potentially lead to toxicity in the spleen. Intravenous administration of PEG-MNPs also enhanced the brain tumor targeting efficiency in the 9L-glioma rat model. MRI and histological analyses also confirmed the targeting efficiency of PEG-MNPs.

Chertok and group investigated the applicability of MNPs tailored with polyethyleneimine (PEI) as a potential drug and gene carrier to the brain tumor [49]. The cationic MNPs (GPEI) exhibited some superior properties such as high cell penetration and low cellular toxicity. Intracarotid administration of GPEI coupled with magnetic targeting, led to the accumulation of NPs in glioma lesions. Also, magnetic accumulation of GPEI was found to be 5.2-fold higher than that of slightly anionic G100 NPs in the tumor lesions. Another study reports the development of SPIONs coated with Bovine serum albumin (BSA-SPIO NPs). The prepared BSA-SPIO NPs were conjugated with tumor-specific ligand folic acid (FA) and then labeled with fluorescein isothiocyanate for intracellular visualization in U251 glioma cells [50]. The developed FA-BSA-SPIO NPs showed excellent biocompatibility, low cytotoxicity and high cellular uptake. Studies showed that after fluorescein isothiocyanate labeling, the developed NPs effectively internalized in the targeted U251 cells that could help in intracellular visualization and MRI.

Real-time monitoring

The monitoring of MNPs inside the body after their application is vital for more specific targeting and diagnosis. Obtaining a high magnetic field gradient, which can offer a high steering force with high monitoring resolution is the biggest challenge for MNP delivery. In 2017, Zhang and coworkers reported a real-time imaging-based guidance system of NPs by means of untethered electromagnetic devices for real-time tracking and guiding [77]. They introduced a new imaging technique that included an electromagnetic actuator and MPI system to navigate NPs in the body in a noninvasive manner. The NPs improved the targeting efficiency and real-time monitoring.

Magnetic particle imaging

Remote magnetic steering is a newly developed technology that represents a powerful platform for the magnetic particle imaging (MPI) system. In comparison to MRI and other methods, MPI provides a higher degree of 3D localization imaging rate and superior forces due to the field gradient greater than 1 $T/m/\mu 0$ [78]. Magnetic control on field image-guided radiation-free devices can be achieved at the clinical scale, which can be useful in diagnosis and therapeutic interventions [79]. Zhang and group developed a soft magnetic core with coils that can increase the magnetic gradient field [80]. However, they observed that it also produces harmonic noise, leading to poor MPI signalling and MNP analysis. However, the developed system was able to perform 1D MNP and 2D MPI transport, with higher image resolution and steering force. In another study, Shao *et al.* defined a rapid and highly sensitive analytical method for profiling circulating microvesicles from the blood samples of glioblastoma patients [81]. The microvesicles labeled with target-specific MNPs were introduced on a smart microfluidic chip and were detected by a nuclear magnetic resonance system. They observed that the novel system had a shallow threshold of detection and could distinguish GBM microvesicles from nontumor host cell-derived microvesicles. Furthermore, the circulating GBM microvesicles can be used to monitor mutations of primary tumors and could serve as a prognostic metric of treatment-induced changes in real-time monitoring of drug delivery.

Hyperthermia

Hyperthermia is a type of medical treatment in which body tissue is exposed to an elevated temperature of up to 40–45°C in order to kill or destroy cancer cells [82]. The tumor cells are less resistant to the abrupt increase in temperature as compared with healthy surrounding cells. Cell membranes are composed of phospholipids and proteins and are very heat sensitive. Hyperthermia can alter the proteins and structures within the tumor cells by inducing various intracellular and extracellular effects such as protein misfolding, changes in potential of hydrogen (pH), induction of apoptosis, reduced perfusion and tissue oxygenation [83]. Hyperthermia also promotes cell membrane permeability, which increases the diffusion of drugs into the tumor cells [84–86]. The effectiveness of cancer treatment by hyperthermia depends on various factors such as characteristics of cancer cells, temperature and duration of exposure at the targeted site. Traditionally, thermal energy was transferred to the cancer cells by external devices using light irradiation or electromagnetic waves. Hyperthermia can also be induced by using conventional

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Table 3. Magnetic nanoparticle-based hyperthermia therapy systems for brain tumors.

Delivery system	Animal model	Cell line	Ref.
Superparamagnetic iron oxide nanoparticle-based hyperthermia	Rat model	Cultured healthy rat astrocytes	[91]
Magnetic nanoparticle-based microRNA and hyperthermia therapy	-	U87-EGFRvIII	[92]
Magnetic hyperthermia (nonpyrogenic magnetosome minerals coated with poly-L-lysine)	Mouse model	U-87 luc glioma	[93]
Magnetic nanoparticles in poly (methyl methacrylate) based hyperthermia	-	U87MG	[86]
IUdR-loaded PCL-PEG-coated magnetic nanoparticles in combination with hyperthermia and ionizing radiation therapy	-	U87MG	[94]
Hyperthermia and chemotherapy using Fe(Salen) nanoparticles.	Mouse model	U251 cells	[95]
Superparamagnetic iron oxide nanoparticles with magnetic hyperthermia	Mouse model	E297 and U87	[96]

PCL: Poly (caprolactone); PEG: Poly (ethylene glycol).

techniques such as microwaves, infrared irradiation, ultrasound [87] and by using hot water tubes [88]. However, there are several limitations of using these techniques such as low heat penetration in the tumor cells, thermal under-dosage at the targeted tumor site, damage to the surrounding healthy tissues and dissipation of heat by the blood that may occur in highly vascularized tumors [89]. Despite many shreds of evidence that proves the effectiveness of heat in treating cancer, hyperthermia is not yet established in clinical routine. The main discrepancies related to hyperthermia are mainly due to technical limitations of the treatment to attain efficient temperature distributions in the body than from lack of efficacy of the treatment [90].

MNP-based hyperthermia therapy

In the past few decades, in order to synthesize MNPs, several types of iron oxides such as magnetite (Fe_3O_4), hematite (α-Fe_2O_3) and maghemite (γ-Fe_2O_3 and β-Fe_2O_3) have been explored [91]. Among MNPs, IONPs have been extensively investigated because of their high heating capacity [86] and distinct magnetic and optical properties, such as coercivity, magnetic susceptibility, high paramagnetism and low Curie temperature [85]. Some of the MNPs based hyperthermia therapy systems for brain tumors are mentioned in Table 3. Schaub *et al.* performed a viability test on cortical astrocytes of the healthy rat using SPIONs [91]. Significant cell death was observed when SPIONs were added to the cultures of cortical astrocyte under the influence of an applied magnetic field. SPIONs, in presence of magnetic field and temperatures up to or more than 45°C reduced astrocyte viability. Tumor treatment with magnetic hyperthermia results in the production of HSPs, whose basic function is to protect protein degradation. Yin *et al.* demonstrated the collective effect of MNP based delivery of miRNA (*let-7a*) on cancer cells, which target the main downstream effectors of HSPs on an MNP platform [92]. MNP based delivery of miRNA (*let-7a*) showed more significant apoptosis in brain cancer cells than either magnetic hyperthermia or *let-7a* treatment alone. Furthermore, targeting of *IGF1R* and RAS pathways by miRNA (*let-7a*) may enhance the caspase-3 mediated apoptosis. The combined MNP-based *let-7a* delivery along with magnetic hyperthermia offers several advantages such as enhancement of transfection by magnetic targeting and possible monitoring of treatment through MRI. In another study, Alphandéry *et al.* reported that by using IONPs, called magnetosomes, the survival of patients with recurrent glioblastoma can be increased [93]. Magnetosomes were synthesized and extracted by magnetotactic bacteria and most of the endotoxins and organic material were removed. These magnetosomes were then coated by poly-L-lysine to form a nonpyrogenic and stable NP suspension, which is characterized by a high heating power as compared with their chemically synthesized counterparts presently used in clinical trials. M-poly-L-lysine showed improved antitumor efficacy in U87-Luc intracranial tumors in mice under the influence of the alternating magnetic field.

Recently, Wu and coworkers developed an aqueous surfactant-free ferrofluid comprising SPIONs coated by silicate meso layers and carbon shells [97]. *In vitro* studies demonstrated the effectiveness of the nanoparticulate ferrofluids in reducing the viability of osteosarcoma and glioblastoma cells, while having the least effects on primary cell lines. The NPs significantly decreased the metastatic migration of the cancer cells in 3D tumor spheroids. Results also revealed that the application of magnetic hyperthermia to NPs treated spheroids reduced the viability of the tumor in contrast to the control group. Both *in vivo* and *in vitro* models of the BBB demonstrated the capability of the prepared NPs to cross the barrier and localize in the brain tissue. Furthermore, developmental studies of flies raised in ferrofluid infused media confirmed the non-toxic nature of the prepared nanoparticulate ferrofluids. Feuser *et al.* developed MNPs coated with oleic acid (MNPs-OA) and later loaded then with polymethyl

Table 4. Miscellaneous magnetic delivery systems for brain tumor targeting.

Delivery system	Drug	Animal model studied	Cell line	Ref.
Magnetic core–shell nanocapsules	Doxorubicin and curcumin	BALB/c female nude	RG2	[99]
Thermosensitive magnetic liposomes	Cetuximab and camptosar	Balb/c nude mice	U87	[100]
Self-assembled pH-sensitive fluoromagnetic nanotubes as archetype system	-	Mouse model	NIH/3T3 fibroblasts	[101]

methacrylate (PMMA0) [86]. The MNPs-PMMA NPs showed no cytotoxicity in murine fibroblast (L929) cells and U87MG cells and, thus, can be used as promising carrier systems for the treatment by hyperthermia.

The clinical response in cancer treatment can be dramatically enhanced by the combination of radiation therapy and hyperthermia. Rezaie *et al.* developed poly (caprolactone)-poly (ethylene glycol) (PCL-PEG) coated MNPs as a delivery vehicle for 5-iodo 2′deoxyuridine (IUdR) and investigated their potential role in the treatment of the glioblastoma cell line under the influence of hyperthermia and X-ray radiation [94]. The authors found that the combination of hyperthermia and radiation significantly reduced the colony number of glioblastoma spheroid cells treated with IUdR-loaded MNPs. In another study, Stauffer *et al.* investigated the possibility of combining hyperthermia and radiation therapy by using a thermobrachytherapy balloon implant filled with MNPs for the treatment of at-risk tissue surrounding the tumor resection cavity [98]. By using numerical modeling, they simulated the temperature distributions in the brain surrounding the thermo brachytherapy balloon for brain blood perfusion. They further constructed a magnetic induction to couple energy into MNPs to heat tissue around the balloon implant. This study demonstrated the feasibility of using a thermo brachytherapy balloon implant for simultaneous heat and radiation treatment of the tumor. Pernal and coworkers dispersed SPIONs in hydroxyapatite (HAP), the mineral component of our bones, increase the uptake in cancer cells and reduces the risk to nearby healthy cells [96]. They found that the uptake of nanocomposites increased cytoskeletal anisotropy in both the primary cancer cells and healthy human mesenchymal stem cells. Furthermore, the treatment of cancer cell with nanocomposites in an alternating magnetic field resulted in hyperthermia effect, which reduced the treated cell population without harming the control population.

Miscellaneous systems

The potential of LF conjugated magnetic double emulsion nanocapsules loaded with drug DOX and curcumin as an efficient drug-delivery system was explored by Fang and groups [99]. The authors found that magnetic guidance increased the cellular uptake of LF conjugated magnetic double emulsion nanocapsules in the RG2 cells that overexpress the LF receptor. Further study showed that intravenous injection of the nanoplatform in mice bearing brain tumor followed by magnetic targeting resulted in high accumulation of the codelivered chemotherapeutics at the targeted site and efficiently suppressed the growth of cancer. Another study reports the development of magnetic and thermal dual responsive thermosensitive magnetic liposomes co-encapsulated with Camptosar (CPT-11) and citric acid-coated magnetic Fe_3O_4 NPs within the aqueous core [100]. Later on, CET was conjugated onto the surface of the nanoplatform for recognizing overexpressed EGFR on the surface of cancer cells. The conjugation of CET onto the surface of the nanoplatform enhanced the intracellular uptake of the prepared system into human primary glioblastoma cells (U87). Positron emission tomography/MRI and *in vivo* imaging system studies confirmed the *in vivo* therapeutic efficiency of thermosensitive magnetic liposomes-CPT-11-CET in mice orthotopic xenograft brain tumor model. Villa *et al.* functionalized ferromagnetic NPs and fluorescent chromophores onto the surface of synthetic chrysotile nanotubes to explore their imaging and brain cancer-targeting efficiency [101]. The acquired magnetic properties permitted their use as a contrast agent for MRI and also enabled tracking of tumor cell migration. The prepared fluoromagnetic nanotubes demonstrated an affinity with the *in vivo* condition and showed the capability to migrate across the BBB after injection. Some of the miscellaneous magnetic delivery systems for brain tumor targeting are listed in Table 4.

Conclusion

Brain tumor remains a formidable treatment challenge despite advancements in surgery, chemotherapy and radiation therapy. The accumulation and retention of drug-loaded nanocarriers at the site of the brain tumor could allow the local release of a drug, thus increasing the exposure to cytotoxic agents at the target site. In recent years, significant advancements in the design and synthesis of MNPs have been achieved. Magnetic targeting has shown remarkable

potential for localized delivery of drug-loaded nanocarriers at the tumor site. Brain tumor targeting using MNPs is a noninvasive strategy and does not hinder normal brain function. Various studies reported in the review indicated that MNPs presents with great potential as a theranostic system for brain tumor targeting.

Future perspective

Magnetic drug delivery is considered a promising technology for the treatment of brain tumor. The delivery systems having a magnetic core, recognition layer and a therapeutic load have great therapeutic potential. There are serious challenges, particularly concerning right combination of receptors and recognition layers. The useful recognition layers must be identified or attached to the particles, and they should be loaded in a high density while maintaining their required character. Magnetic hyperthermia is also a promising technique for the treatment of brain tumor, but its use has been limited by the fact that the tumor needs to be localized. As a result, this route cannot be used in preventive medicine or for the treatment of early-stage tumors. Another challenge presented by MNPs is the requirement of the high magnetic field gradient that can provide high monitoring resolution.

Some significant issues need to be considered while selecting MNPs for drug delivery, such as the fate of the MNPs after the drug delivery and the related side effects. Compatibility of the shell materials and drug with each other must be considered while loading drugs into NPs, or else a burst effect could generate toxic materials due to the combination of drug and shell materials. Rejection of MNPs by the human body, biocompatibility problems and toxicity related to the NPs can be overcome soon by an in-depth understanding of the interactions between biomolecules and MNPs in the living systems, which can further lead to the development of novel MNPs with favourable surface properties.

Executive summary

Background

- Brain tumor or intracranial tumor is an abnormal mass of tissue that multiplies in an abnormal way in the brain and can directly destroy healthy cells of the brain.
- Brains tumors are generally divided into glioma and nonglioma tumors. Gliomas are the most common type of primary brain tumor in adults.
- Temozolomide is the first-line drug for the treatment of high-grade brain tumors, especially anaplastic astrocytoma and glioblastoma.

Magnetic nanoparticles for diagnosis & treatment of tumor

- Magnetic nanoparticles (MNPs) such as iron oxide nanoparticles (NPs), superparamagnetic iron oxide NPs and fluorescent MNPs are widely used as diagnostic imaging agents and therapeutic delivery vehicles.
- MNPs can play numerous functions at the same time, including multimodal imaging drug delivery, real-time monitoring and combined therapeutic methodologies.
- Drug targeting to the required site by using the magnetic delivery system is based on the force exerted by the particles and magnetic force generated by the external magnet.

Real-time monitoring using MNPs

- The monitoring of MNPs inside the body after their application is vital for more specific targeting and diagnosis.
- Obtaining a high magnetic field gradient, which can offer a high steering force with high monitoring resolution is the biggest challenge for MNP delivery.

MNP-based hyperthermia therapy

- Hyperthermia is a type of medical treatment in which body tissue is exposed to an elevated temperature of up to 40–45°C in order to kill or destroy cancer cells.
- Among MNPs, iron oxide NPs have been extensively investigated for hyperthermia therapy because of their high heating capacity and distinct magnetic and optical properties, such as coercivity, magnetic susceptibility, high paramagnetism and low Curie temperature.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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