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Review

Potential for Treatment of Glioblastoma: New Aspects of Superparamagnetic Iron Oxide Nanoparticles

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Abstract. *Glioblastoma (GB) is a highly aggressive and infiltrative brain tumor characterized by poor outcomes and a high rate of recurrence despite maximal safe resection, chemotherapy, and radiation. Superparamagnetic iron oxide nanoparticles (SPIONs) are a novel tool that can be used for many applications including magnetic targeting, drug delivery, gene delivery, hyperthermia treatment, cell tracking, or multiple simultaneous functions. SPIONs are studied as a magnetic resonance imaging tumor contrast agent by targeting tumor cell proteins or tumor vasculature. Drug delivery to GB tumor has been targeted with SPIONs in murine models. In addition to targeting tumor cells for imaging or drug-delivery, SPION has also been shown to be effective at targeting for hyperthermia. Along with animal models, human trials have been conducted for a number of different modes of SPION utilization, with important findings and lessons for further preclinical and clinical experiments. SPIONs are opening up several new avenues for monitoring and treatment of GB tumors; here, we review the current research and a variety of possible clinical applications.*

Glioblastoma (GB) represents the most common and most aggressive type of primary brain tumor in adults with a nearly uniform fatal outcome. Despite multimodal therapy, including maximal safe surgical resection of the tumor with adjuvant chemotherapy and radiation, the overall survival time remains about 15 months (1). GB tumors are heterogeneous with genetic and epigenetic variation within the tumor mass. These aspects make the development of therapies to eradicate the entire tumor a challenging task. Conventional therapeutic strategies include surgery followed by chemotherapy and radiation. Some chemotherapy regimens may include temozolomide, monoclonal antibodies against vascular endothelial growth factor (VEGF), or inhibitors of tyrosine kinase receptors (1, 2). Poor outcome and recurrence is largely attributed to: a) the highly aggressive and infiltrative nature of GB tumors which may increase the likelihood of subtotal resection; b) limited delivery of therapeutics across the blood–brain barrier (BBB); and c) glioma stem cells that contribute to formation, expansion, recurrence, and therapy resistance resulting in tumor recurrence (3).

To enhance the efficacy of treatment and drug delivery, several strategies have been developed. One strategy focuses on the utilization of superparamagnetic iron oxide nanoparticles (SPIONs). SPIONs in brain cancer treatment are an attractive modality for several reasons. They can be used for magnetic targeting, drug delivery, gene delivery, hyperthermia treatment, and cell tracking (4-9).

The SPION core is usually made of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3), and the surface of superparamagnetic core is covered with a compatible coating such as dextran, polyethylene glycol (PEG), poly-L-Lysine, D-mannose, or other different polymers to prevent agglomeration and to enhance biocompatibility (10-13). Active molecules can be bound to the coating, which is used to tailor the nanoparticle for specific applications, *e.g.* active targeting (9). SPIONs are prepared by different methods, with co-precipitation being the one most often used (14). However, different methods, including sol-gel process, hydrothermal method, thermal

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decomposition, microemulsion system, high energy ball mining process and microwave-assisted synthesis are also utilized. More detailed description of SPION preparations has been reviewed elsewhere (15).

SPIONs as Contrast Agent in Tumor Imaging

Magnetic resonance imaging (MRI) is a crucial clinical imaging technique for precise diagnosis of central nervous system (CNS) diseases, including GB. SPIONs are an attractive tool for MRI of brain tumors, since they act as a negative contrast agent, enhancing the image contrast by reducing the T2 MRI signal (Figure 1A). Further improvement in relaxivity can be achieved by tuning the core size and coating (Figure 1B). Tong *et al*., using 14 nm core and PEG1000 coating, achieved T2 relaxivity of 385 s^{-1} mM^{-1}, which is among the highest per Fe atom (16). The recent development of nanocarriers has significantly improved sensitivity in conventional MRI. The need to enhance agent accumulation in tumor vasculature is highly urgent for noninvasive, visual presentation of cancer aggressiveness and guidance of GB excision and can be met by these nanocarriers. To improve tumor imaging specificity, different ligands and bioactive substances that can recognize target receptors present in the cancer cells can be carried on the SPION surface (Figure 1C). Several tumor ligands, including lactoferrin, neuropilin-1, epidermal growth factor receptor (*EGFR*) deletion-mutant (EGFRvIII), are often utilized as potential candidates for active tumor targeting (17). Surface modification with chitosan increased the surface charge of dextran-coated SPIONs, resulting in their enhanced internalization in GB cells. In addition, high MRI contrast-enhancing properties for defining a brain tumor can be achieved by hybrid chitosan-dextran SPIONs (18). To identify patients who might benefit from EGFR-targeted therapies, lipid-encapsulated SPIONs conjugated with anti-EGFR cetuximad were prepared. The EGFR-SPIONs preferentially targeted cell lines with high EGFR expression. Similarly, a dual-mode molecular imaging probe was made by conjugating a short peptide, identical to the deletion junction of EGFRvIII (PEPHC1) and which can exclusively bind to EGFRvIII, to PEGylated SPIONs with near infrared fluorescence dye cyanine 7 monosuccinimidyl ester (also called cyanine 7.5 ester), signifying an improvement in MRI sensitivity, along with the spatial resolution of optical imaging. Indeed, in *in vitro* and *in vivo* experiments, both MRI as well as optical imaging showed better sensitivity when using this nanoprobe to identify and characterize GB tumors with EGFRvIII mutation (19). To selectively image tumor vasculature, insulin-like growth factor-binding protein 7 (IGFBP7), which is a selective and abundantly expressed biomarker of human GBM vessels, was chosen as a target. Several studies demonstrated that IGFBP7 is overexpressed

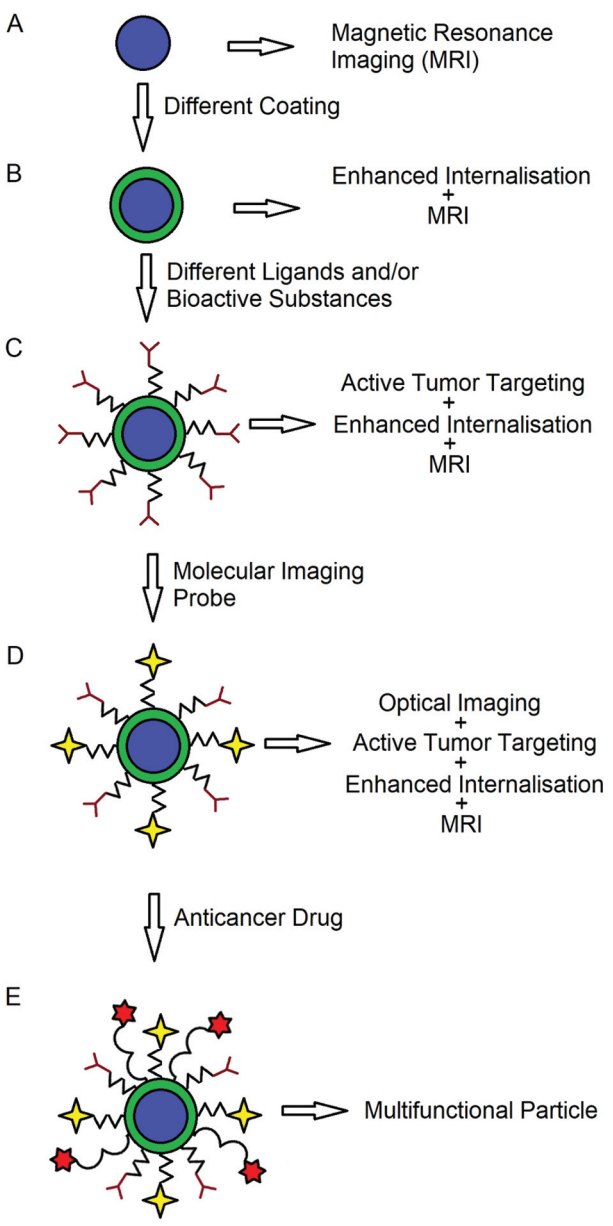

Figure 1. *Superparamagnetic nanoparticles (SPION) are composed of a metallic core for magnetic resonance imaging (A) which can be coated with biocompatible polymers to enhance tumor internalization (B). Further surface functionalization with bioactive compounds enables active tumor targeting (C). Combining SPIONs with near-infrared fluorescent dyes creates dual-mode imaging probes (D). Embellishing SPION surfaces with anticancer drugs generates effective nanocarrier systems (E).*

in tumor blood vessels, with little or no expression in normal blood vessels (20, 21). Cell-specific single-domain antibody against IGFBP7 was conjugated to dextran-coated SPIONs. Because the diagnostic efficacy of molecular imaging can be enhanced by application of multimodal contrast agents, the

SPION was also bound to an infrared marker to produce a multifunctional particle (Figure 1D). The accumulation of the contrast agent in the tumor was demonstrated with *in vivo* optical imaging and MRI, and its localization in tumor vessels was confirmed with immunohistochemistry of brain sections (22). SPIONs conjugated with interleukin 1 receptor antagonist can serve not only as an efficient contrast agent for tumor *in vivo* imaging, but can significantly reduce peritumoral edema, which often contributes to neurological syndromes (23).

SPIONs as a Carrier for Drug Delivery

SPIONs not only provide enhanced contrast for diagnostics using MRI but may also help direct release of chemotherapeutic agents at the site of tumor (Figure 1E). Hollow structured SPIO nanoshells were used as carriers for intracellular delivery of hydrophobic anticancer drugs. SPIO nanoshell-based encapsulation provided a stable aqueous dispersion of curcumin. Intracellular curcumin content delivered via curcumin-SPIO was 30-fold higher than free drug delivery. Doxorubicin encapsulated in SPIO nanoshells enhanced caspase-3 activity two-fold compared with free drug (24). Doxorubicin bound to SPION reduced cell proliferation *in vitro* of primary GB cell lines isolated from patient's biopsy at 10 nM, while free doxorubicin was effective at 50 nM. Moreover, a low concentration of doxorubicin bound to SPION did not negatively affect growth of healthy non-tumorous cells (25). SPIONs are often loaded into polymer nanoparticles together with an anticancer drug to create effective nanocarrier systems. Paclitaxel and SPIONs were loaded into poly lactic-co-glycolic acid-based nanoparticles. Endocytosis of SPION-paclitaxel by the U251 GB cell line led to inhibition of cell proliferation and migration, and induced programmed cell death via apoptosis modulated by reactive oxygen species and autophagy with the accumulation of autophagosomes (26). Similar construction of nanocarriers was prepared for *in vivo* study. An external magnet was placed over the head of mice with orthotopic GB. Due to disrupted BBB in mouse, nanoparticles with SPION- paclitaxel enter the brain and their uptake was further enhanced by magnetic targeting. This treatment resulted in higher antitumor activity with an improved survival rate as compared to control animals, treated by passive targeting only or saline (27). Vincristine, a microtubule-interfering chemotherapeutic agent, is extensively used as a potent anticancer agent. However, vincristine is a fast-metabolized drug that also causes severe nerve toxicity, which restricts its clinical use. A recent study has focused on the creation of monoclonal antibody to CD-133 (CD133mAb)-targeted immunomagnetic albumin microbeads primarily to improve the antitumor activity of vincristine. Here, first SPIONs were prepared as nanocarrier cores, which were encapsulated with albumin and then VCR was loaded to achieve better treatment of GB. Furthermore, CD133mAb possess specific affinity for membrane-bound CD133, which subsequently conjugates to form CD133mAb-bearing therapeutic immunomagnetic albumin microbeads, called (CD133mAb/TMAMbs). These CD133mAb/TMAMbs were then taken up by the U251 cell line, which highly expresses the CD133 transmembrane protein. Microbeads have high drug-loading capacity, excellent hemocompatibility and displayed enhanced inhibitory activities against GB including antiproliferative activity, reduction of cell viability and migration, induction of apoptosis, disruption of cytoskeleton organization and overproduction of reactive oxygen species (28). Instead of targeting CD133 surface protein, antibody against nestin can be utilized. SPION-based polymeric nanocomposites encapsulating temozolomide was tagged with antibody against nestin, and then with transferrin/polysorbate-80, allowing them to pass through the BBB and to target GB cells. It is important to note that efficacy of the nanocomposite resulted in improved permeability across the BBB, providing better therapeutic and targeting as demonstrated in *in vivo* studies. Moreover, enhanced GB tumor cell death can be achieved by constant release of temozolomide from the nanocomposite (29).

SPION-mediated Hyperthermia

SPIONs can be used not only for MRI, but also for magnetic particle-mediated hyperthermia, during which SPION exposure to an alternating magnetic field increases the local temperature to induce necrosis. Magnetic hyperthermia, which is produced by SPIONs conjugated with targeting agents or drugs, can be more effective in anticancer therapy than single treatment alone. For tumor-specific hyperthermia, several targeting agents were tested. Magnetic hyperthermia in cultured cells was induced by SPIONs conjugated with specific anti-human epidermal growth factor receptor (HER2) aptamer. High specificity toward the HER2-expressing cells was achieved using aptamer-tagged SPIONs. An approximately 50% decrease in cell viability due to hyperthermia was achieved by 90-fold lower dose of the tagged SPIONs, which should greatly limit the side-effects of treatment (30). To increase the efficiency of hyperthermia treatment, SPIONs were coated with aminosilane, which prolonged survival of rats bearing brain tumor by 4.5-fold over dextran-coated SPIONs. Similarly, hydroxyapatite/SPION nanocomposites increased the uptake ratio between U87 human brain cancer cells and non-tumorous cells, suppressed migration in a primary brain cancer spheroid model and reduced cell viability as compared to groups treated with SPIONs alone, without affecting the viability of non-cancerous cells. Moreover, treatment of cancer cells with an alternating magnetic field for 30 min caused a severe hyperthermic effect, which led to suppression of the cell population by more than 50%, without affecting control

populations (31). It is important to note that combined cancer chemotherapy and hyperthermia can be accomplished by SPIONs. Thermosensitive magneto-liposomes that contained SPIONs and doxorubicin were designed for *in vitro* and *in vivo* therapy of C6 rat glioma. The results showed that magneto-liposomes can be specifically heated to 43˚C in a few minutes, and during this, the encapsulated doxorubicin is released in a controllable manner. The *in vitro* experiments showed that cell viability decreased to 17.3% after heat treatment with doxorubicin release. The *in vivo* results established that magnetic drug targeting combined with doxorubicin release had a robust inhibitory effect on GB, with tumor volume growth suppression and complete regression (32). Combination of hyperthermia with ionizing radiation might also be beneficial in antitumor therapy. Numerous studies have shown that 72 kDa stress-inducible heat-shock protein (HSP70) is expressed exclusively on the membrane of high-grade gliomas. It can be targeted with SPIONs conjugated with HSP70-specific antibody (cmHSP70.1). This SPION–cmHSP70.1 conjugate can recognize membranous HSP70, which aids in assessing tumor-specific targeting prior to ionizing irradiation. Furthermore, a seven-fold increase in the tumor-to-normal brain uptake ratio of SPION–cmHSP70.1 conjugate in GB-bearing rats was rendered by biodistribution analysis as compared to SPION treatment alone. In addition, a single dose (10 Gy) of ionizing radiation was shown to further increase the accumulation of SPION–cmHSP70.1 conjugate in HSP70-positive GB (33). The radiosensitizing efficacy of gold and SPION-loaded micelles (GSM) coated with glycol-polycaprolactone polymer was tested. GSM administration in conjunction with radiation therapy led to ~2-fold increase in density of double-stranded DNA breaks (34). Therapeutic efficacy of antitumor therapy can be improved by the synergic effect of drug delivery increased by folate, radiosensitivity enhanced by paclitaxel and absorption of proton energy increased by SPIONs (35). For imaging-guided photothermal therapy, bifunctional nanoparticles (BFNPs) comprised of a SPION core covered by a fluorescent carbon shell were developed. BFNPs demonstrate dual-modal imaging capacity both *in vitro* and *in vivo*, with fluorescent imaging excited under a varying wavelength from 405 nm to 820 nm and with T2-weighted MRI. More significantly, BFNPs absorb and convert near-infrared light to heat, enabling photothermal therapy as demonstrated mice bearing C6 GB (36).

SPIONs in Clinical Trials and Future Outlook

Recent advances on preclinical studies show promise for the future, however, clinical applications are emerging slowly. So far SPIONs are mainly used in clinical trials for hyperthermia induction. First studies were published in 2001, showing feasibility and safety of this treatment (37). Post-mortem study on patients with GB who underwent hyperthermia therapy revealed that numerous nanoparticles were disseminated or present in aggregated clusters in the tumor tissues. The necrotic regions were limited to areas of SPION application, which showed the necessity to saturate the tumor with SPIONs. It was also found that internalization of the nanoparticles was mainly driven by macrophages and not by tumor cells (38). In a recent study, patients with recurrent GB (n=6) were subjected to intracavitary thermotherapy after coating the tumor resection cavity wall with SPIONs. These patients were given 1-h hyperthermia sessions six times in an alternating magnetic field. Furthermore, in certain instances, patients also received simultaneous fractionated radiotherapy (39.6 Gy). Intestinally, no major adverse effects were seen with this treatment, however, tumor-flare reactions with noticeable edema around the nanoparticle deposits was evident in computed tomographic scan several months later. These patients were subjected to either dexamethasone treatment or surgical removal of the nanoparticles. The treated area was void of tumor activity, although necrosis was evident around aggregated nanoparticles, as observed from the histopathological results. In addition, increased expression of caspase-3 and HSP70, $CD3^+$ T-cells, along with infiltration by SPION-bearing macrophage was noted in the immunohistochemical study. In addition, augmented intracellular ratios of interferon gamma to interleukin-4 in $CD4^+$ and $CD8^+$ memory T-cells, plus activation of tumor-associated myeloid cells along with microglia with enhanced human leukocyte antigen-DR isotype and programmed death-ligand, was evident in tumor cells using flow cytometric detection. This enhanced HSP70 expression in hyperthermia may imply modification of the levels of major histocompatibility complex class I molecules on tumor cells as it translates to intrinsic as well as adaptive immunity. These changes may lead to an activation of pro-inflammatory cytokines as well as adhesion molecules, causing enhanced infiltration of immune cells into the tumor tissue, Most importantly, two patients achieved durable treatment responses for nearly 2 years with no additional therapy. Hence, using SPIONs in intracavitary thermotherapy in conjunction with radiotherapy provides a sustainable treatment modality for recurrent patients with GB (39). Preclinical studies have confirmed the versatility of SPIONs not only for *in vivo* imaging, but also for active targeting, drug delivery and hyperthermia as well as complementary therapy.

To synopsize, in recent years, awareness of cancer nanomedicines has gained substantial momentum leading to the discovery of SPIONs. They may represent an appropriate candidate for a new-generation MRI contrast agent, but also a tool for therapeutic intervention to treat deadly disease like GB. Nanotechnology has spawned colossal aptitude in the diagnosis and treatment of cancer. Therefore, the use of SPION in oncology provides wide range of advantages; from serving as carriers of chemotherapeutic drugs to radiosensitizers, contrast agents and photothermal therapeutics. Furthermore, they have

become an integral part of theranostics that combines therapeutics and diagnostics.

Conflicts of Interest

All Authors declare no competing financial interest.

Authors' Contributions

PJ, MJ, CG contributed to the concept of the article and PJ, MJ, CG helped to draft and develop the article. DM, KT, TS contributed to the writing of article. All Authors read and approved the final draft of the article.

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