

Magnetic nanoparticles in cancer diagnosis, drug delivery and treatment (Review)

MEIJIA WU and SHENGWU HUANG

Department of Pharmacy, Zhejiang Chinese Medical University, Hangzhou, Zhejiang 311402, P.R. China

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Abstract. In recent years, magnetic nanoparticles (MNPs) have demonstrated marked progress in the field of oncology. General nanoparticles are widely used in tumor targeting, and the intrinsic magnetic property of MNPs makes them the most promising nanomaterial to be used as contrast agents for magnetic resonance imaging (MRI) and induced magnetic hyperthermia. The properties of MNPs are fully exploited when they are used as drug delivery agents, wherein drugs may be targeted to the desired specific location *in vivo* by application of an external magnetic field. Early diagnosis of cancer may be achieved by MRI, therefore, individualized treatment may be combined with MRI, so as to achieve the precise definition and appropriate treatment. In the present review, research on MNPs in cancer diagnosis, drug delivery and treatment has been summarized. Furthermore, the future perspectives and challenges of MNPs in the field of oncology are also discussed.

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1. Introduction

Magnetic nanoparticles (MNPs) are a kind of intelligent nanomagnetic material, with small particle size, large specific surface area, magnetic response and superparamagnetism (1). MNPs may be assembled and positioned under a constant magnetic field, and the heat is absorbed by the electromagnetic wave in the alternating magnetic field. In biomedical applications,

MNPs are generally in the superparamagnetic state (2,3). The most frequently used nanomaterial is the iron oxide nanoparticle, including magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$) (4). It is well known that MNPs have an important role in cancer diagnosis, drug delivery and treatment. For cancer diagnosis, tumor imaging technology opened the possibility of early detection of disease. Common imaging modalities include magnetic resonance imaging (MRI) (5), magneto acoustic tomography (MAT) (6), computed tomography (CT) (7) and near-infrared (NIR) imaging (8). Among them, MRI has a strong influence in the early diagnosis of cancer, and superparamagnetic iron oxide nanoparticles (SPIONs) are the most representative as a contrast agent for MRI (9). Currently, certain iron oxide-based MNPs have been approved for use in clinical MRI, for example ferumoxil (GastroMARK) enhances imaging of the bowel (10). Due to the small size and large specific surface area of MNPs, they are able to easily reach the location of the lesion (11). Therefore, MNPs as a drug carrier for drug delivery is an application that cannot be ignored. This property of MNPs is fully exploited when they are used as drug delivery agents, wherein drugs may be targeted to the desired specific location *in vivo* by application of an external magnetic field (12). In general, MNPs are used as drug carriers by binding antibodies (13) and chemotherapeutic drugs (14). Commonly, chemotherapeutic drugs are loaded in MNPs, and they are involved in cancer treatment. MNPs in the field of cancer therapy are generally used in several different ways: Chemotherapy; magnetic hyperthermia (MHT) (15); photodynamic therapy (PDT) (16); and photothermal therapy (PTT) (17). In order to achieve an improved therapeutic effect, the general method used is combination therapy. The present review provides a framework for the application of MNPs in medicine, such as cancer diagnosis, drug delivery and treatment. Furthermore, nanotoxicity is also reviewed, as well as the potential challenges and the opportunities.

2. Cancer diagnosis

When cancer is discovered earlier, the cure rate is greatly improved. Therefore, early detection and timely diagnosis of cancer is key to reduce the mortality rate of patients (18). Tumor imaging technology has an important role in cancer diagnosis and the choice of late clinical treatment options. Furthermore, MNPs are the contrast agents that are most widely researched and used in cancer imaging. Here, the imaging methods and the imaging positions of MNPs are discussed.

Correspondence to: Professor Shengwu Huang, Department of Pharmacy, Zhejiang Chinese Medical University, Gaoke Road, Hangzhou, Zhejiang 311402, P.R. China
E-mail: hsw55@163.com

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Imaging methods

MRI. Due to the high spatial resolution and tomographic capabilities of MRI, it has been considered to be one of the most valuable noninvasive imaging techniques (19), and MNPs have been recently proposed as a contrast agent for MRI (20). In general, in order to overcome the colloidal instability of MNPs, it is necessary to conduct surface modification of nanoparticles (NPs) by inducing the magnetic dipole interaction and its intrinsic surface energy (21). For example, water-dispersible polyethyleneimine (PEI)-coated Fe_3O_4 NPs were prepared, and then sequentially modified with PEGylated folic acid (FA) and fluorescein isothiocyanate (FI) via PEI mediated conjugation chemistry (21). The remaining PEI surface amines were subjected to acetylation to form the colloiddally stable FA-functionalized Fe_3O_4 NPs for MRI (21). In MRI, research has demonstrated that early lesion detection of a 6-year old boy with glioblastoma multiforme may be achieved by sensitive imaging of superparamagnetic NPs or aggregates (22). Furthermore, research on Au nanorod@polypyrrole@iron oxide (Au NR@PPy@Fe₃O₄) nanocomposites has demonstrated that these systems exhibit a low r_2/r_1 ratio of 4.8, making them efficient T1 positive contrast-enhancing agents for MRI (19). The study also indicated that the multifunctional nanocomposites exhibited the potential of the combination of therapeutic and diagnostic features (23).

Other imaging methods. A study by Mariappan *et al* (6) presented magneto acoustic tomography, which uses magnetomotive force due to a short pulsed magnetic field to induce ultrasound in SPION-labeled tissue and estimates an image of the distribution of the NPs *in vivo* with ultrasound imaging resolution. Magnetic particle imaging (MPI) allows high spatial resolution and sensitivity as a tomographic imaging technology. A study by Lindemann *et al* (24) suggested that University of Luebeck Dextran-coated SPIONs are a promising tracer material for use in innovative tumor cell analysis in MPI. In addition, photoacoustic imaging has gained increasing attention as a potential imaging tool. A study by Li *et al* (25) developed a new generation of magnetomotive photoacoustic featuring cyclic magnetic motion and ultrasound speckle tracking, whose imaging capture frame rate is several hundred times faster than the photoacoustic speckle tracking method that has previously been demonstrated (26). Stone *et al* (8) demonstrated a magnetic NP system that may be used to observe the NP fate within a biofilm using NIR imaging. Additionally, Xi *et al* (27) presented a breast imaging technique combining high-resolution NIR light induced photoacoustic tomography (PAT) with NIR dye-labeled amino-terminal fragments of urokinase plasminogen activator receptor-targeted magnetic iron oxide NPs (NIR830-ATF-IONP) for breast cancer imaging using a murine model of orthotopic mammary cancer. Other studies have demonstrated that ultrashort echo time (UTE) imaging (28) and MPI (29) may improve the detection of MNPs in cancer.

For MNPs, in addition to MRI, other imaging methods are used in combination. This dual imaging method may improve the accuracy of diagnosis. For instance, dual imaging of single-photon emission computed tomography (SPECT) and MRI has been utilized in pancreatic (4) and breast (30) cancer. A study by Jang *et al* (31) demonstrated the synthesis and the use of monodisperse iron oxide NPs coated with fluorescent silica nano-shells for fluorescence and magnetic resonance dual

imaging of tumors. Furthermore, Sun *et al* (32) utilized MRI and optical imaging (OI) for the diagnosis of breast cancer.

Imaging position

Pancreas. Pancreatic cancer is one of the most lethal cancers in the world due to its late presentation (33). Therefore, early diagnosis will increase the cure rate of patients. When chitosan-coated MNPs and survivin antisense oligonucleotides (ASON) are conjugated to give Sur-MNPs, the MNPs functionalized with ASON lead to targeted localization in pancreatic tumors (34). Survivin-targeted NPs could be used by MRI for detection of pancreatic tumors (34). Taking into account the more sensitive diagnostic tools to allow early medical imaging, biodegradable NPs prepared using recombinant human serum albumin and incorporated iron oxide (maghemite, $\gamma\text{-Fe}_2\text{O}_3$) NPs were developed (4). Improved targeting and imaging properties were demonstrated in mice using SPECT-CT and MRI (4).

Breast. A study by Bucci *et al* (35) outlined some guidelines for the design of the imaging device for MNPs to enhance the microwave imaging of breast cancer. The results demonstrated that MNP-enhanced microwave imaging may reliably detect cancer lesions even using low-complexity arrangements, when designed according to the devised guidelines. An investigation by Kato *et al* (36) concluded that liposome encapsulation significantly improved the delivery and retention of SPIONs in breast tumors, and targeted SPION liposomes have significantly improved accumulation in breast tumors, which could be the optimal option for MRI detection of breast tumors. With magnetic nanoclusters coated with ruthenium (II) complexes doped with silica (fluorescent magnetic NPs; FMNPs), Sun *et al* (32) demonstrated that more peptide cyclic-arginine-glycine-aspartic acid (RGD)-FMNPs accumulated around the tumors than FMNPs. The result indicated the potential application of RGD-FMNPs as a targeting molecular probe for detection of breast cancer using MRI and OI (32). In order to make more accurate and specific diagnosis of breast cancer, Bevacqua and Scapaticci (37) adopted a compressive sensing approach for three-dimensional breast cancer microwave imaging. In their paper, an *ad hoc* compressive sensing algorithm was developed by exploiting the knowledge of the maximum concentration of MNPs that may be targeted in human tissues (37).

Prostate. MRI provides the best soft tissue resolution and has an important role in the management of prostate cancer as it is the recommended imaging modality for patients with prostate cancer (38). Sentinel lymph node (SLN) evaluation in patients with prostate cancer is commonly performed via lymphoscintigraphy following injection of radiolabeled tracers (39). For example, patients underwent MRI at 1.5 T before and 1 day after SPION injection using T1-, T2- and T2*-weighted sequences (39). This was the first study to use intraprostatic injection of SPIONs to visualize SLNs by MRI in patients with prostate cancer (39). A study by Winter *et al* (40) indicated that using a transrectal intraprostatic injection of SPIONs for magnetic marking in prostate cancer is safe, feasible and reliably identifies SLNs and lymph node metastases in the majority of patients. In other cases, diffusion-weighted (DW)-MRI is sensitive to water diffusion throughout tissues, which correlates with the Gleason score, a histological measure of prostate cancer aggressiveness (40).

Table I. Specific circumstances of imaging and treatment modalities.

Author, year	Imaging method	Treatment modality	Treatment site	(Refs.)
Wang <i>et al</i> , 2014	MRI	PDT	Head and neck	(44)
Bhattacharya <i>et al</i> , 2016	MRI	Targeted therapy	Head and neck	(45)
Pilapong <i>et al</i> , 2014	MRI	Targeted therapy	Liver	(46)
Wu <i>et al</i> , 2015	MRI	PTT	Liver/cervical	(47)
Azhdarzadeh <i>et al</i> , 2016	MRI	PTT	Colon	(48)
Yu <i>et al</i> , 2015	MRI/photoacoustic tomography	PTT	Liver/cervical	(49)
Zhou <i>et al</i> , 2015	MRI/photoacoustic imaging	Photothermal ablation	Breast	(50)
Lin <i>et al</i> , 2015	MRI/fluorescence imaging	Targeted therapy	Cervical	(51)
Wang <i>et al</i> , 2014	MRI/ fluorescent imaging	Targeted therapy	Stomach	(13)
Li <i>et al</i> , 2015	MRI/infrared thermal imaging	Chemotherapy/MHT	Liver	(52)
Kim <i>et al</i> , 2016	MRI/optical imaging	PDT/MHT	Melanoma	(53)
Sun <i>et al</i> , 2016	MRI/computed tomography	Targeted therapy	Brain	(54)
Zhao <i>et al</i> , 2014	Near-infrared fluorescence imaging	PDT	Head and neck	(55)

MRI, magnetic resonance imaging; PDT, photodynamic therapy; PTT, photothermal therapy; MHT, magnetic hyperthermia.

The incorporation of DW-MRI-based prostate cancer stratification and monitoring could increase the accuracy of preclinical trials using mice with transgenic adenocarcinoma of the mouse prostate (41).

Lung. To improve the sensitivity of detection of metastasis of lung cancer, Wan *et al* (42) created immune SPIONs used in magnetic resonance immune imaging. These SPIONs were coated with oleic acid and carboxymethyl dextran, and then conjugated to mouse anti-cluster of differentiation (CD) 44v6 monoclonal antibody (42). The prepared SPIONs are potentially useful for lung tumor-targeting diagnosis. In addition, targeted pulmonary inhalation aerosol-based delivery facilitates the direct application of drugs to the lungs in a controlled manner, and has inherent advantages (43). Therefore, Nishimoto *et al* (29) investigated the feasibility of applying MPI to pulmonary imaging using nebulized MNPs and to quantify the mucociliary clearance in the lung, using small animal experiments.

Other. Common contrast agents are frequently used in the pancreas, breast and prostate. In other cases, the diagnosis and treatment are carried out in combination, with a variety of imaging modalities, as outlined in Table I.

3. Drug delivery

Magnetic targeted drug delivery has been used to improve the therapeutic performance of drugs and reduce the side effects associated with the conventional treatment of cancer. MNPs coated with a stabilizing shell have been successfully used as contrast agents for MRI (56). On the basis of early diagnosis, the treatment may be carried out at the same time, and the efficiency may be greatly improved. Therefore, MNPs are essential for drug delivery. By binding antibodies, chemotherapeutics or other drugs, MNPs may be used as drug carriers.

Antibodies. Research has demonstrated that antibody-conjugated MNPs may not only be used for detection of ovarian cancer biomarkers, but may also treat ovarian cancer due to their high-level accumulation within cancer cells (57,58). A study by Wang *et al* (13) reported, for the first time, that anti- α -subunit of adenosine triphosphate synthase antibody, HAI-178 monoclonal antibody (mAb)-conjugated fluorescent MNPs, was successfully used for targeted imaging and simultaneous therapy of *in vivo* gastric cancer. As for human breast cancer, Shanehsazzadeh *et al* (59) demonstrated disappointing *in vivo* results that had very low accumulation of nanoprobe in the targeted site when conjugating ultra-small SPIONs with C595 mAb. On the contrary, a study by Rasaneh and Dadras (60) suggested that combining MNPs and a permanent magnet may increase the therapeutic efficacy of herceptin for increased accumulation in the tumor site.

In order to improve the therapeutic efficiency, the combination of antibodies and chemotherapeutic drugs is attracting increasing attention. A study by Aires *et al* (61) presented a novel multi-functionalized iron oxide MNP with anti-CD44 antibody and gemcitabine derivatives, and their application for the selective treatment of CD44-positive cancer cells. In addition, Huang *et al* (62) developed an ovarian cancer dual-targeting therapy involving magnetic Fe₃O₄ NPs grafted with single-chain antibody and docetaxel loaded β -cyclodextrin. These studies have demonstrated the great potential of the combination of antibodies and chemotherapeutic drugs.

Chemotherapeutic drugs. Commonly used chemotherapy drugs include doxorubicin (DOX), paclitaxel, cisplatin, gemcitabine, methotrexate, docetaxel, sorafenib and mitomycin C, as outlined in Table II. DOX is the most widely applied chemotherapy drug in targeted delivery systems (63). MNPs have limits in their stability because of hydrophobic coating (64). To address this issue, a reducible copolymer self-assembled

Table II. Various chemotherapeutic drugs delivered through magnetic nanoparticles.

Author, year	Drug	Polymer modification	Average size, nm	Cancer cell line	(Refs.)
Zohreh <i>et al</i> , 2016	Doxorubicin	Starch-g-poly (methyl methacrylate-co-PEG-acrylamide)	93	HeLa	(67)
Frounchi and Shamshiri, 2015		Poly (lactic acid)/PEG	22	-	(68)
Bhattacharya <i>et al</i> , 2016		Polyethyleneimine cross-linked Pluronic F127 copolymer	~91	HeLa	(45)
Pilapong <i>et al</i> , 2014		Carboxymethyl	5	K562/ADR	(69)
Wu <i>et al</i> , 2014		APS-PEG-TFEE	20	MCF-7	(70)
Chandra <i>et al</i> , 2015		L6-PEG-PAMAM and S6-PEG-PAMAM	9.6±0.13	-	(71)
Hałupka-Bryl <i>et al</i> , 2015		PEG-poly (4-chloromethylstyrene)	8-12	-	(72)
Zou <i>et al</i> , 2015		Chitosan	~120	MCF-7	(73)
Tansik <i>et al</i> , 2014		PLGA	74	MCF-7	(74)
Ghorbani <i>et al</i> , 2016		Poly (N-isopropylacrylamide-co-IA)	30	HeLa	(75)
Mangaiyarkarasi <i>et al</i> , 2016	Paclitaxel	Chitosan	19-37	A549	(76)
Lin <i>et al</i> , 2015		Poly[(N-isopropylacrylamide-r-acrylamide)-b-L-lactic acid]	229.0±13.2	HeLa	(77)
Fazilati, 2014	Cisplatin	Heparin	45±15	CP70	(78)
Parsian <i>et al</i> , 2016	Gemcitabine	Chitosan	4	SKBR; MCF-7	(79)
Roy <i>et al</i> , 2016	Methotrexate	Poly (N-isopropyl acrylamide)-co-tyrosine	10-15	MCF-7	(80)
Nagesh <i>et al</i> , 2016	Docetaxel	Cyclodextrin and F127 polymer	139.5±2.16	C4-2	(81)
Li <i>et al</i> , 2015	Sorafenib	PEGylated PLGA	205±3.12	BEL7402	(82)
Türkmen <i>et al</i> , 2014	Mitomycin C	Poly (hydroxyethyl methacrylate)	200	-	(83)
Unsoy <i>et al</i> , 2014	Bortezomib	Chitosan	5-7	HeLa; SiHa	(84)

PEG, polyethylene glycol; APS-PEG-TFEE, Polyethylene glycol dicarboxylic acid; PLGA, Poly (DL-lactic-co-glycolic acid).

with SPIONs was developed to deliver DOX for cancer therapy (14). The copolymer of reducible polyamidoamine with polyethylene glycol/dodecyl amine graft was synthesized by Michael addition (14). Additionally, research has demonstrated that the application of iron oxide MNPs improved DOX-NP cell penetration compared to free DOX and achieved a cellular response to DOX-NP conjugates similar to that of DOX alone (65). SPIONs have also been investigated as a carrier for targeted drug delivery. For example, Cicha *et al* (66) set up an *in vitro* system to analyze the different aspects of cellular responses to mitoxantrone-carrying SPIONs and to the drug released from SPIONs.

Other. In addition to chemotherapy drugs, some traditional Chinese medicine monomers have been utilized as anti-cancer drugs in targeted drug delivery. A study by Nigam and Bahadur (85) demonstrated the fabrication and characterization

of dendrimerized MNPs as delivery vectors for epigallocatechin gallate. Recently, curcumin has been widely applied in the drug delivery of MNPs in breast and ovarian cancer. A study by Mancarella *et al* (86) developed a layer by layer functionalization of Fe₃O₄ NPs by coating them in Dextran and Poly(L-lysine), which obtained a high upload of curcumin in Fe₃O₄ NPs for treating ovarian cancer. Furthermore, magnetic Fe₃O₄@zirconium phosphate core-shell NPs and magnetic Fe₃O₄@hydroxyapatite-PEI-b-cyclodextrin NPs have been demonstrated to be effective drug carriers for the delivery of curcumin, and these were both used to treat breast cancer (87,88).

In other cases, oligonucleotides are applied in drug delivery. A study by Pourianazar and Gunduz (89) utilized three-layer MNPs composed of a Fe₃O₄ magnetic core, an aminosilane interlayer and a cationic poly(amidoamine) dendrimer, which enhanced the accumulation of CpG-oligodeoxynucleotides

molecules in tumor cells as a novel targeted delivery system. Furthermore, 2-amino-2-deoxy-glucose was conjugated to -COOH-modified cobalt ferrite MNPs, which were designed to target tumor cells as a potential targetable drug/gene delivery agent for cancer treatment (90). In summary, MNPs may provide a high-efficiency drug delivery system with the potential to achieve drug targeting.

4. Cancer treatment

As a drug carrier, the ultimate goal of MNPs is to treat. This section discusses and provides examples of the use of MNPs in MHT, PDT, PTT and combined treatment.

MHT. MHT has attracted a lot of interest in recent years due to its potential use in medicine. MNPs are able to convert electromagnetic energy into heat (91). Therefore, the most popular application for MNPs is most likely the destruction of tumor cells by heating them to their apoptosis threshold (92). Magnetic field strength and frequency, NP size, NP concentration and solution viscosity are important parameters and may improve the efficiency of heat generation for effective cancer therapy while administering a low NP treatment dose (93). Although MNPs represent an area of active development for MHT, the *in vivo* anti-tumor effect under a low-frequency magnetic field using MNPs has not yet been demonstrated. A study by Cheng *et al* (94) demonstrated the successful use of spin-vortex, disk-shaped permalloy magnetic particles in a low-frequency, rotating magnetic field for the *in vitro* and *in vivo* destruction of glioma cells. In addition, the hysteresis loss is also important for MHT, as increasing the hysteresis loss is improving the heating efficiency (94). A study by Sasayama *et al* (95) examined the hysteresis loss of magnetically fractionated MNPs for hyperthermia application. They concluded that the efficiency of hyperthermia is improved by magnetically separating MNPs (95). Generally, MHT may enhance the efficacy of chemotherapeutic drugs to some degree. For instance, by combining SPIONs (MF66) functionalized with Nucant multivalent pseudopeptide (N6L), DOX and MHT, the therapeutic effects of MHT in breast cancer could be strongly enhanced (96). Furthermore, dual-functional Pt-Fe-hydroxyapatite MNPs were developed for chemo-hyperthermia treatment of lung cancer (97). In addition, research has indicated that MHT of MNPs enhanced radiation therapy in murine models of human prostate cancer (98). In other cases, gene delivery also has an important role in MHT (99,100).

PDT. PDT is an externally-activated and minimally invasive modality for cancer treatment. The process of PDT involves the systemic or local application of photosensitizing drugs, called photosensitizers (PSs), followed by photoexcitation of the PSs in the tissue using light of the appropriate wavelength and power (16). In the presence of oxygen, the PS is excited from the ground state to the excited state following activation with light of an appropriate wavelength, and an electron is transferred to nearby tissue oxygen, producing oxygen free radicals or excited singlet oxygen (101). These substances are also known as reactive oxygen species (ROS) (102,103), which cause cell damage, and eventually lead to cancer tissue damage. To enhance the effect of PSs, building a targeted drug delivery

system with MNPs has become of interest. For instance, a study by Park *et al* (104) synthesized multifunctional cobalt ferrite (CoFe_2O_4) NPs [CoFe_2O_4 -hematoporphyrins (HPs)-FAs] functionalized by coating them with HP for introducing photo-functionality and by conjugating with FA for targeting cancer cells. Furthermore, other research has revealed that the Fe_3O_4 @HP particles demonstrated remarkable and efficient photodynamic anticancer activity, and exhibited strong anti-cancer effects on human prostate cancer (PC-3) and breast cancer (MDA-MB-231) cell lines (105). Pyropheophorbide-a (PPA) as a novel chlorin PS was prepared for PDT. PPA-coated multifunctional magneto-fluorescent NPs, Fe_3O_4 @ SiO_2 @CS@PPA (MFCSPPA) were designed (106). The experiments demonstrated that MFCSPPA had strong photodynamic therapy activity and low dark toxicity, and cell viability of human HeLa cervical cancer cells was reduced to 18% following treatment with PDT (106).

PTT. As a light absorbent of low toxicity on skin and deep tissue penetration, NIR may directly kill cancer cells by PTT, which has become a controlled treatment method (107). PTT using photothermal agents in combination with NIR has also gained increasing attention for cancer treatment (108). An example of this is engineering phosphopeptide-decorated MNPs as efficient photothermal agents for solid tumor therapy (109). Notably, the photothermal effect of MNP clusters was initially reported for the photothermal ablation (PTA) of tumors *in vitro* and *in vivo*. Compared with individual magnetic Fe_3O_4 NPs, clustered Fe_3O_4 NPs may result in a marked increase in NIR absorption (17). Upon NIR irradiation at 808 nm, clustered Fe_3O_4 NPs inducing higher temperatures were more cytotoxic against A549 cells (17). In the majority of cases, PTT and MRI are carried out in combination (110,111). However, a study indicated that, compared with their large counterparts, small Fe_3O_4 NPs exhibited greater cellular internalization, thus enabling a higher PTA efficacy *in vitro* (112). In addition, 120 nm may be the optimal diameter of Fe_3O_4 NPs for MRI and PAT *in vitro* (112). Therefore, the size of MNPs may be an important factor for PTT.

Combined treatment. In general, MNPs act as drug carriers for targeted delivery systems. The nanocomplex with PTT agents and PSs together may be used for combined cancer PTT and PDT. A study by Bhana *et al* (113) demonstrated the first application of magnetic-optical hybrid nanosystems for magnetic-field-guided drug delivery and dual mode PTT and PDT. The composite NPs may generate heat and ROS simultaneously upon NIR laser irradiation, and may even be selectively delivered to the mitochondria (114). Furthermore, MNPs have been demonstrated to have the dual capacity to act as both magnetic and PTT agents for amplification of heating efficiency (115). In conclusion, these results demonstrated high accumulation of MNPs in tumors and excellent tumor regression.

5. Conclusions and perspectives

MNPs as contrast agents of imaging have a great potential in adjuvant therapy. However, due to some toxicity being associated with the use of MNPs, many restrictions have been

applied in their application. Surface coatings of MNPs are known to influence advantageous features of MNPs, as well as potential toxicity. Research has indicated that the larger the size of the MNPs, the greater the accumulation *in vivo*. Therefore, controlling the size and surface coatings of MNPs could reduce toxicity and improve magnetic behaviors.

In the present review, we focused on cancer diagnosis by imaging, drug delivery and treatment using MNPs. Despite many successful studies using MNPs as a theranostic material, there are still some challenges. While many MNP formulations have demonstrated excellent results in small animal models, they cannot reach the clinical requirement. By focusing on improving their drug loading capacity, and increasing their specificity and affinity to target cancer cells, MNPs may become suitable for clinical use with integrated imaging and multimodal therapy in the near future and dramatically impact the treatment of cancer.

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