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Magnetic nanoparticles based cancer therapy: current status and applications

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Nanotechnology holds a promising potential for developing biomedical nanoplatforms in cancer therapy. The magnetic nanoparticles, which integrate uniquely appealing features of magnetic manipulation, nanoscale heat generator, localized magnetic field and enzyme-mimics, prompt the development and application of magnetic nanoparticles-based cancer medicine. Considerable success has been achieved in improving the magnetic resonance imaging (MRI) sensitivity, and the therapeutic function of the magnetic nanoparticles should be given adequate attention. This work reviews the current status and applications of magnetic nanoparticles based cancer therapy. The advantages of magnetic nanoparticles that may contribute to improved therapeutics efficacy of clinic cancer treatment are highlighted here.

magnetic nanoparticles, therapeutic delivery, magnetic hyperthermia treatment, theranostics

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INTRODUCTION

Increasing interest has been devoted to applying nanotechnology to cancer medicine due to its unique features for drug delivery, diagnosis and therapy (Blanco et al., 2015; Fan et al., 2017; Chen et al., 2017; Shi et al., 2017; Ni et al., 2017). Thanks for the tremendous efforts that have been made to nanomedicine in the past decades, several therapeutic nanoparticle platforms such as liposomes and albumin nanoparticles have been approved for cancer treatment thus far (Shi et al., 2017). In comparison with these organic nanoparticles, inorganic nanoparticles have more diverse and distinct physical properties closely correlated to their size and composition (Alivisatos, 1996; Link and El-Sayed, 1999; Jun et al., 2008). As demonstrated by the approved nanomedicine, the successful applications of nanoparticle-based cancer therapy lie in smart design of the nanoparticle with tailoring properties for safer and more effective cancer treatment. Among various inorganic nanoparticle formulations investigated, magnetic iron oxides nanoparticles exhibit not only high biocompatibility but also an integrated design capability for cell targeting, imaging and therapy (Pankhurst et al., 2003; Lee et al., 2007). Several magnetic nanoparticle-enable imaging modalities are now under clinical investigation (Mienkina et al., 2009). In addition, recent advance has shown its intrinsic capability of activating immune response (Mikhaylov et al., 2011) and inhibiting tumor growth (Mikhaylov et al., 2011; Zanganeh et al., 2016). Moreover, the magnetic nanoparticle platforms can produce localized heat under alternating magnetic field which may

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act as the switching for controlling cell signaling at molecular level (Huang et al., 2010; Stanley et al., 2012; Chen et al., 2015). All of these features make the magnetic nanoparticles a promising biomedical nanoplatform in cancer therapy.

The fundamentals of magnetic nanoparticles for cancer therapy lies in the four unique characteristics: magnetic manipulation, nanoscale heat generator, localized magnetic field and enzyme-mimics with abundant active sites (Figure 1). With the advantages of these fundamentals, various magnetic nanoparticle based cancer therapies have been developed (Liu et al., 2015; Hervault and Thanh, 2014; Kim et al., 2017; Ho et al., 2011; Yoo et al., 2011). For example, when an external alternating current (AC) magnetic field is applied, thermal energy can be produced through repeated alignments of magnetic spins (Néel relaxation) and physical rotation (Brownian relaxation) of a magnetic nanoparticle (Hervault and Thanh, 2014). Magnetic hyperthermia therapy can thus be realized by localized heat generated by magnetic nanoparticle for regional tumor treatment (Liu et al., 2015; Lee et al., 2011). Benefiting from the deep tissue penetration of electromagnetic wave, this approach can treat tumor deep inside the brain (Chen et al., 2015), while the intrinsic therapeutic effect of magnetic nanoparticles takes the advantages of the Fenton's reaction on the surface of iron oxide nanoparticles to regress the tumor growth (Zanganeh et al., 2016).

In this review, we summarize the recent advance in magnetic nanoparticle-based cancer therapy. Not only will we highlight the advantages and fundamentals of magnetic nanoparticles for cancer therapy, but also some new understandings of the role of magnetic nanoparticles in cancer nanomedicine will be discussed.

MAGNETISM FOR BIOMEDICAL MAGNETIC NANOPARTICLES

The magnetic materials are usually characterized by the parameters magnetization (M), coercivity (H_c), and magnetocrystalline anisotropy constant (K). Saturation magnetization (M_s) is the maximum magnetization value of a material under a high magnetic field. Coercivity (H_c) is the strength of the external magnetic field to make the magnetization value of subjective materials zero. Magnetocrystalline anisotropy is the tendency of the magnetization to align itself along a preferred crystallographic direction of easy axis. The magnetocrystalline anisotropy constant (K) is a physical constant which reflects the energy required to change the direction of magnetization from easy to hard axis. The bulk magnetite (Fe_3O_4) is multi-domain ferrimagnetic materials. When the size of the particles is smaller than a certain critical size, spins of free electrons within the nanoparticles are aligned into one direction and the nanoparticles act as a single-domain magnet. The alignment of magnetization directions within each single-domain is controlled by the anisotropy energy KV (V is the domain volume). As the nanoparticle size decreases, thermal energy k_BT (k_B is Boltzmann constant and T is temperature) overtakes KV (V is the volume of nanoparticles), resulting in superparamagnetic behavior with randomized magnetization directions and zero coercivity (Figure 2A). The zero coercivity of a superparamagnetic nanoparticle is essential for biomedical application where no residual magnetization is critical to minimize the magnetic dipole-dipole interaction between the nanoparticles. This facilitates the formation of a stable colloid solution (Wu et al., 2016). The magnetism of magnetic nanoparticle shows size- and shape-dependence. For example, the ferrimagnetic vortex-domain iron oxide nanorings (FVIOs) show a unique magnetic structure, in which the magnetization is circumferential to the ring without stray fields. Without the external field, the FVIOs show a vortex state with negligible remanence and coercivity, which can greatly reduce dipole-dipole interactions and enable a good colloidal stability. When an external field is applied, FVIOs will undergo transition from a vortex state to an onion state and move along the field direction rapidly (Figure 2B). The saturation

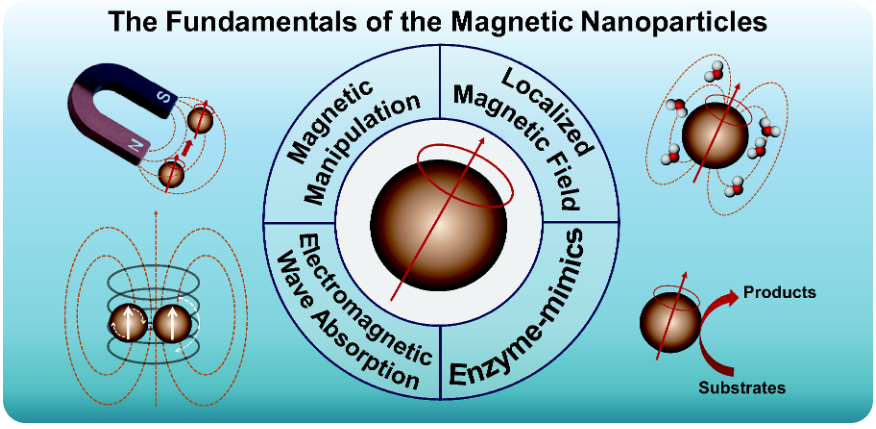

Figure 1 (Color online) The fundamentals of the magnetic nanoparticles.

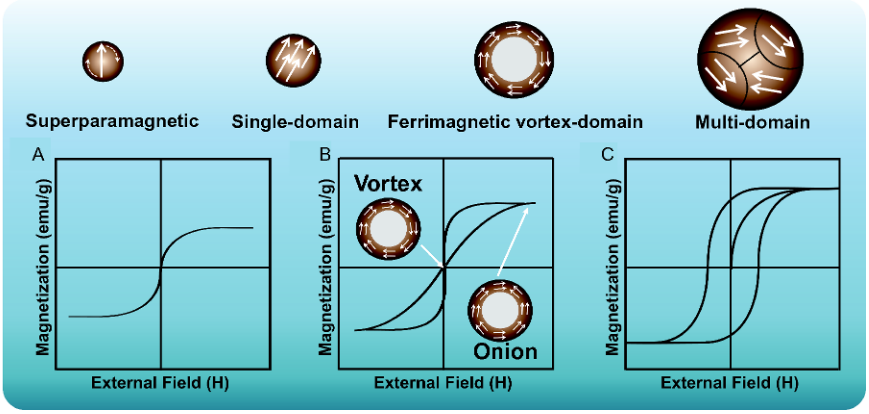

Figure 2 (Color online) The hysteresis loop for the (A) superparamagnetic (B) ferrimagnetic vortex-domain and (C) multi-domain nanoparticle.

magnetization of the FVIOs is much higher than that of superparamagnetic iron oxide nanoparticles (Liu et al., 2015).

INTRINSIC THERAPEUTIC EFFECT

It has been a long history that people believe the magnetite can be a cure for the ailments. In modern medicine, the therapeutic effects of the nanoparticle are usually realized by carrying chemical or biological drugs or executing physical treatment such as hyperthermia (Hervault and Thanh, 2014; Lee et al., 2015). Although the application of the intrinsic effect of the inorganic nanoparticles themselves on diseases proves to be a valuable approach (Arvizo et al., 2012), the underlying mechanism is still unclear. The intrinsic therapeutic effect of magnetic nanoparticle will not only make it a promising "nanomedicine", but also shed a new light on how the complex interaction between nanoparticles and cells impacts cancer growth and evolution.

Song et al. investigated the biological effects of 10 nm iron oxide nanoparticles on neuro-2a cells. The results showed that the iron oxide nanoparticles can trigger cell cycle arrest at G0/G1 phase; while the enhancement of ROS production is closely related with the nanoparticles induced endoplasmic reticulum (ER) stress response (Wang et al., 2014). Recently, Daldrup-Link and his colleagues have offered a new strategy for cancer treatment. They demonstrated that the FDA-approved iron oxide nanoparticles (ferumoxytol) can kill cancer cells through a ROS-dependent mechanism, announcing the "Iron Age" is coming for cancer therapy (Tarangelo and Dixon, 2016). In this work, ferumoxytol actually showed no direct cytotoxic effects on cancer cells at clinically relevant doses. However, co-cultures of cancer cells, macrophages and ferumoxytol showed an 11-fold increase in hydrogen peroxide and a 16-fold increase in hydroxyl radical production in comparison with that without ferumoxytol. It was proven that the iron oxide nanoparticles induced a phenotypic shift of macrophages from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype. This polarization then evoked the Fenton reaction of the iron oxide nanoparticles, resulting in the production of ROS and the cancer cell apoptosis (Figure 3). *In vivo* results further showed a significantly suppressed tumor growth (57% at 21 days post-inoculation; P=0.038) of ferumoxytol co-implanted cancer cells compared with non-ferumoxytol-treated controls. Thus, the macrophage polarization induced by ferumoxytol is a mechanism for its intrinsic therapeutic effects in cancer therapies (Zanganeh et al., 2016).

THERAPEUTIC DELIVERY

The intrinsic limits (high cytotoxicity, poor water solubility, multiple-drug resistance and poor specificity) of the traditional chemotherapeutic drugs make them difficult to deliver sufficient quantities of drugs to the tumor sites without risk of systemic toxicity (Cho et al., 2008; Cheng et al., 2012). The design and application of drug carriers for effective therapeutic delivery to the tumor sites is attracting growing attention (Arruebo et al., 2007; Peer et al., 2007; Mura et al., 2013). The tumor microenvironment is different from that of the surrounding of normal cells. Fast-growing cancer cells show a high metabolic rate. As the supply of oxygen and nutrients is usually not sufficient to feed their growth, tumor cells use glycolysis to obtain extra energy which further leads to an acidic microenvironment (Hanahan and Weinberg, 2011). Moreover, the tumor microenvironment generally presents a higher concentration of the physiological reducing agent glutathione (GSH). The GSH concentration in some tumor cells has been found at least four times higher than that in normal cells, which causes a redox environment in tumors (Ballatori et al., 2009; Meng et al., 2009). Therefore, it is possible to design stimuli-responsive drug delivery systems based on these features to specifically target tumors.

The use of magnetic particles as carriers for drug delivery started in the 1970s. However, all these earlier magnetic

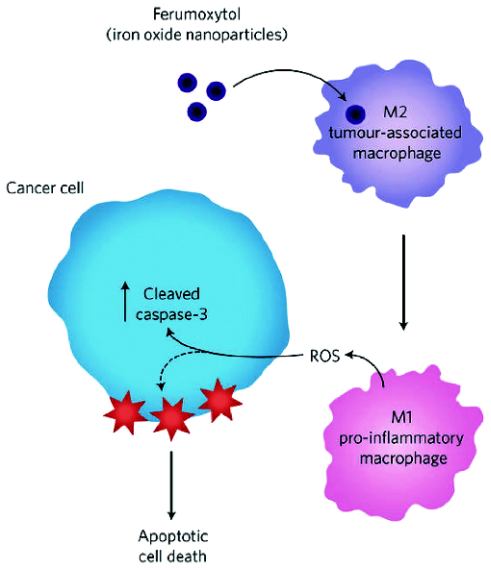

Figure 3 (Color online) The FDA-approved iron oxide nanoparticle drug (ferumoxytol) changes the polarization of tumour-associated macrophages from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 phenotype. M1 polarized macrophages potentially release ROS, which may induce apoptotic cell death characterized by an increase in cleaved caspase-3 (with permission from Tarangelo and Dixon, 2016).

carriers were microsized particles (Arruebo et al., 2007). Thanks for the rapid development in nanoparticle synthesis and surface chemistry, monodispersed magnetic nanoparticles with well-controlled size, composition and surface can be easily prepared harboring both effective drug loading and stimuli-responsive functions. All these advances have promoted the application of the magnetic nanoparticles as drug carriers in past decades. The potential advantages of magnetic nanoparticles as a new paradigm in cancer treatment stem from (i) the unique properties of their magnetic cores combined with high drug loading capability; (ii) the flexible biochemical properties that can be obtained by means of a suitable and biocompatible coating; (iii) the high tumor-specific delivery efficacy minimizing severe side effects; (iv) the programmed release of drugs via specific stimuli, either exogenous (temperature, light or magnetic field) or endogenous (pH, enzyme concentration or redox gradients); (v) the capability of magnetic nanoparticle as MR probes for the real-time monitoring of the drug delivery.

One of the major problem in drug delivery is the poor site-specific delivery efficiency. In order to improve the delivery efficiency and reduce the potential toxicity, the magnetically-controlled drug targeting strategy is often used. For example, Huhn et al. reported a magnetic fluid loaded cytokines that could be delivered to specific organism by high-energy magnetic fields. The magnetic nanoparticles bound with mitoxantrone was also successfully used in targeting squamous cell carcinoma in rabbits via magnetically-controlled drug delivery (Lübbe et al., 1996).

In addition, effective tumor-targeting drug delivery systems require "zero release" before reaching the targeted sites, hence, a stimuli-responsive system will be highly desirable, especially for the delivery of highly toxic antitumor drugs. Magnetic nanoparticle carriers can realize remote control of drug release via pH, redox environment, high-frequency magnetic field and magnetic induction heat once it was delivered to a specific site. Jon et al. reported a pH sensitive doxorubicin-loaded thermally cross-linked superparamagnetic iron oxide nanoparticle (Dox@TCL-SPION). The Dox could be incorporated in the polymeric shell of TCL-SPION through electrostatic interactions between positively charged Dox and the negatively charged polymer coating layers (Figure 4A), and approximately 60% of the drug was released within 50 min at pH 5.1 in acetate buffer (Yu et al., 2008). Sun et al. reported that the pH-responsive porous hollow nanoparticles (PHNPs) of Fe_3O_4 can be exploited as a cisplatin delivery vehicle for targeted therapeutic applications of breast cancer SK-BR-3 cells (Figure 4B). Acidic etching of the PHNPs resulted wider pore gaps on the particles, which then facilitates the release of cisplatin. At pH 5.0, the cisplatin release is four-times faster than that at physiological condition (pH 7.4) (Cheng et al., 2009). Lin et al. reported a redox-responsive delivery system that is composed of a disulfide linked MCM-41-type mesoporous silica nanorods (MSNs) and the Fe_3O_4 nanoparticles. The disulfide linkages can be cleaved by various cell-produced antioxidants and disulfide reducing agents, resulting in the release of the magnetic nanoparticle caps from the MSNs which then triggered escapes of the guest molecules in the matrix (Giri et al., 2005). The high-frequency magnetic field (HFMF) and the magnetic induction heat also can be used in stimuli-responsive release of drugs. Chen et al. reported magnetic silica-based nanospheres as effective drug carriers for controlled release of the guest molecules by magnetic heat. The HFMF accelerates the rotation of magnetic nanoparticles and the induced heat energy subsequently enlarges the nanostructure of the silica matrix to produce porous channels that cause the drug to be released easily (Hu et al., 2008). He also used the iron oxide core coated with thermosensitive hydrogel shell to encapsulate anticancer agent. When inductive heat is generated by iron oxide nanoparticle under external HFMF, the thermosensitive polymer around the iron oxide nanoparticles collapse, resulting in an accelerative drug release (Liu et al., 2008) (Figure 4C). Smyth et al. reported that the magnetic nanoparticles can induce heat-responsive release of fluorophore bimane amine from the surface of superparamagnetic iron oxide nanoparticles (SPIONs) in the presence of oscillating magnetic fields (McGill et al., 2009). Liu et al. reported a core/shell nanocarrier with a drug-containing silica core surrounded by a single-crystalline iron oxide shell. The thin iron oxide shell prevents uncontrollable release of drugs due to natural dif-

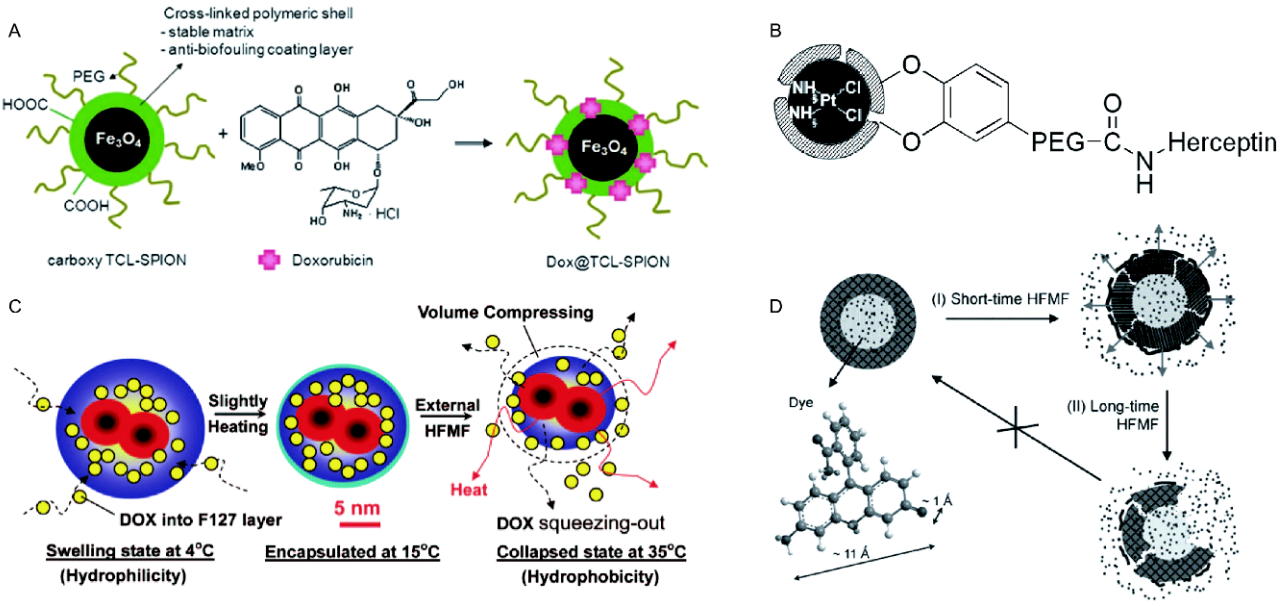

Figure 4 (Color online) Magnetic nanoparticles as drug carriers. A, Formation of Dox@TCL-SPIONs (with permission from Yu et al., 2008). B, Schematic illustration of cisplatin loading into a PHNP and functionalization of Herceptin (with permission from Cheng et al., 2009). C, Proposed mechanism for drug encapsulation and release process of iron oxide nanoparticles coated with thermosensitive hydrogel shell (with permission from Liu et al., 2008). D, Schematic illustration of the thin shell with a proposed mechanism for controlled release of the fluorescence dye (with permission from Hu et al., 2008).

fusion. When the core/shell nanocarrier is subjected to the high-frequency magnetic field, the nanoscale cracks were evolved along the boundary regions of the thin iron oxide shell, allowing dye molecules to be released easily (Hu et al., 2008) (Figure 4D). Therapeutic resistance is one of the major clinical problems and remains a persistent hurdle for disease treatments. Cheon et al. reported a thermoresistance-free apoptosis-inducing magnetic nanoparticle (RAIN). The RAIN consists of heat shock protein (Hsp) inhibitor and magnetic nanoparticle (MNP). When the alternating magnetic field (AMF) is applied, the RAIN simultaneously generates heat and releases the Hsp inhibitor to block the protective function of Hsp which eventually leads to a more effective apoptosis (Yoo et al., 2013).

Gene therapy, which involves manipulating the defective genes that cause diseases, is a promising minimally invasive approach that is of great interest. One approach in gene therapy involves delivering small interfering RNA (siRNA) to interfere with the expression of a specific disease-causing gene. The magnetic nanoparticles are highly attractive platform materials for siRNA delivery owing to their unique properties which include good biocompatibility, superior imaging characteristics, facile surface modification and enhancement of transfection efficiency under the magnetic field. Tada et al. reported the LipoMag, which are assembled as oleic acid-coated magnetite nanocrystal cores with cationic lipid shells, can be used as a highly efficient, magnet-guided gene delivery system. LipoMag achieved a better gene transfection efficiency and gene silencing effect than the commercially available polymer-coated magnetic nanocrystals (Namiki et al., 2009). The oscillating magnet arrays are also reported to show promise for enhancing the overall efficiency of magnetofection (Dobson, 2006). Moreover, the magnetic nanoparticle based gene carriers accumulated in the tumor site can be monitored using MRI (Kievit et al., 2009; Lee et al., 2009; Kievit et al., 2010).

HYPERTHERMIA TREATMENT

Hyperthermia generally refers to a rise in body temperature. For cancer therapy, hyperthermia treatment refers to a moderate rise in temperature (ranging from 41 to 46°C), which leads to cell death through the initiation of a series of pro-apoptotic and apoptotic signaling cascades (Harmon et al., 1991). When the temperature is above 46°C, irreversible cellular damage would occur through necrosis, a process known as thermoablation (Ahmed and Goldberg, 2011). Magnetic nanoparticles are capable of transforming electromagnetic energy to heat. The heat generated by magnetic nanoparticles under external AMF is attributed to their hysteresis dissipation, where the amount of the energy loss is determined to the area of the hysteresis loop (Wu et al., 2016; Hervault and Thanh, 2014).

Magnetic particles were firstly used for hyperthermia treatment by heating lymph nodes in dogs in 1957 (Gilchrist et al., 1957). In 1979, Gordon et al. introduced "intracellular" hyperthermia treatment of cancer (Gordon et al., 1979). Injection of micro-scaled ferromagnetic particles into renal carcinomas of rabbits for hyperthermia treatment was re-

ported by Rand et al. in 1981 (Rand et al., 1982). Clinical studies of magnetic hyperthermia were started in 2007 by Jordan et al. to evaluate the feasibility and tolerability of the newly developed thermotherapy using magnetic nanoparticles on recurrent glioblastoma multiforme. The results show thermotherapy using magnetic nanoparticles was tolerated well by all patients with minor or no side effects. Thus, deep cranial thermotherapy using magnetic nanoparticles can be safely applied on glioblastoma multiforme patients (Maier-Hauff et al., 2007). In 2009, Deimling et al. presented the first postmortem neuropathological study of three patients with glioblastoma undergoing magnetic hyperthermia treatment (MHT). After application of the MHT, survival ranged from 2.1 to 7.9 months (van Landeghem et al., 2009). Clinical hyperthermia treatment of prostate cancer using magnetic nanoparticles has been performed to evaluate the technique of magnetic fluid hyperthermia for minimally invasive treatment of prostate cancer (Johannsen et al., 2005). Morbidity and quality of life during thermotherapy using magnetic nanoparticles in locally recurrent prostate cancer has been investigated in clinical phase I trial. The magnetic nanoparticle deposits were detectable in the prostates one year after thermal therapy. At a median follow-up of 17.5 months, no systemic toxicity was observed. Treatment-related morbidity was moderate and quality of life was only temporarily impaired, indicating the magnetic hyperthermia treatment was feasible and well tolerated in patients with locally recurrent prostate cancer (Johannsen et al., 2007; Johannsen et al., 2010). Recently, magnetic hyperthermia has achieved a great success in clinics (Johannsen et al., 2007). It has been approved in Europe for the treatment of brain tumors. Furthermore, the advanced clinical trials of magnetic hyperthermia for treating prostate tumor are currently under investigation (Salunkhe et al., 2014). The advantages of magnetic hyperthermia for cancer treatment lie in (i) the magnetic nanoparticles can produce localized heat when exposed to an AMF; (ii) the AMF can penetrate into deeper tissues than other heat-generating sources (i.e., light or acoustic waves).

Currently, poor transfer efficiency of magnetic nanoparticles and insufficient heat at tumor site are the main challenges for magnetic hyperthermia treatment. The delivery route of magnetic nanoparticles significantly affects its concentration in tumor and the efficacy of treatment. The intratumoral and intravenous injections are the main approaches used to deliver magnetic nanoparticles (Laurent et al., 2011). Direct intratumoral injection has been effectively applied to anatomically accessible solid tumors with sufficient dosage for magnetic hyperthermia; however, it cannot be used to treat inaccessible primary tumors or metastasis. In these cases, intravenous injection may be used instead, but the main issue with this approach is that the amount of the nanoparticle accumulated in the tumor sites is too less to generate sufficient heat for hyperthermia treatment.

Tailoring the magnetic properties of the magnetic nanoparticles is a popular way to optimize heat conversion efficiency. The specific absorption power (SAR) or specific loss power (SLP) has often been used to evaluate the heating capabilities of magnetic nanoparticles in AMF. According to the theoretical equation that the heat dissipation relies on the magnetic properties of nanoparticles (e.g., saturation magnetization M_s, the effective anisotropy, and solvent viscosity), SLP optimization can be achieved via varying these parameters for an AMF under a given amplitude and frequency (Lee et al., 2015; Fortin et al., 2007). These key magnetic parameters have been optimized by controlling the size, composition, and shape or by constructing heterostructures.

The SLP has a linear correlation with the M_s when the nanoparticles is within superparamagnetic size regime. The SLP of γ-Fe_2O_3 nanoparticles is increased by two orders of magnitude (4 to 275 W g^{-1}) as the M_s becomes larger via the diameter change of γ-Fe_2O_3 nanoparticles from 5.3 to 10.2 nm (Fortin et al., 2007). The SLP also can be tuned by the effective anisotropy (K), which includes magnetocrystalline-anisotropy (K_v) and surface-anisotropy (K_s). Magnetocrystalline anisotropy of magnetic nanoparticle plays an important role in hysteresis dissipation, which can be tuned by the composition and interface/surface engineering (Lee et al., 2015). For example, Cheon et al. synthesized the Zn and Mn doped ferrite nanoparticles for increasing the magnetocrystalline anisotropy. The SLP value of Zn and Mn doped ferrite nanoparticles is four times higher than that of Ferridex (Jang et al., 2009). Another case in tuning magnetocrystalline anisotropy is to utilize the exchange anisotropy which is interfacial exchange interaction between hard and soft magnetic phases. Designing the exchange-coupled magnetic nanoparticle as high-performance magnetic hyperthermia agent through a magnetically hard core and soft shell to maximize the SLP is the representative work in this field (Figure 5A and B). The coercivity enhancement is a feature in such nanoparticle system caused by an exchange anisotropy energy via the interfacial interactions. The core-shell cube comprised of $Zn_{0.4}Fe_{2.6}O_4$ core (50 nm in edge) and $CoFe_2O_4$ shell (5 nm in thickness) exhibits significantly increased H_c of 1900 Oe, which is 14 times larger than that of the regular cube (H_c=140 Oe). This further leads to a significantly enhanced SLP value (Noh et al., 2012). The exchange-coupled $CoFe_2O_4$@$MnFe_2O_4$ nanoparticles have been employed to test the efficacy of antitumor hyperthermia therapy. The in vivo results indicate a high anti-cancer hyperthermia efficiency of the exchange-coupled nanoparticles, as the tumor subjected to 10 min hyperthermia treatment with these particles was eliminated on day 18, while the tumor size of the untreated group increased ninefold during the same period (Lee et al., 2011) (Figure 5C and

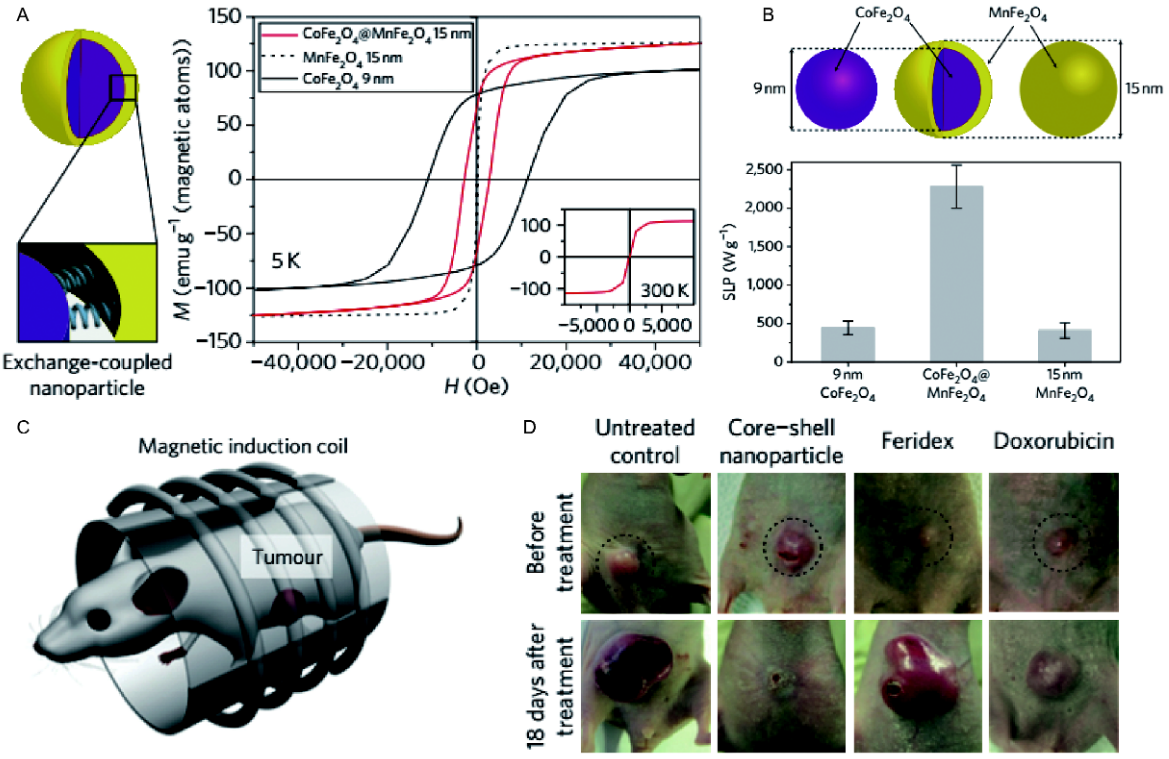

Figure 5 (Color online) Exchange-coupled magnetic nanoparticle as high-performance magnetic hyperthermia agent. A, (Left) Schematic drawing of core-shell nanoparticle with an exchange-coupled magnetism, and (Right) M-H curve of 15 nm $CoFe_2O_4$@$MnFe_2O_4$, 15 nm $MnFe_2O_4$ and 9 nm $CoFe_2O_4$ nanoparticles measured at 5 K using a SQUID magnetometer. The magnetization curve of the core-shell nanoparticle (red curve) shows the hard-soft exchange-coupled magnetism with a smooth hysteresis curve. Inset: M-H curve of $CoFe_2O_4$@$MnFe_2O_4$ at 300 K, showing its superparamagnetic nature with zero coercivity. B, Schematic of 15 nm $CoFe_2O_4$@$MnFe_2O_4$ nanoparticle and its SLP value compared with the values for its components (9 nm $CoFe_2O_4$ and 15 nm $MnFe_2O_4$). C, Schematics of *in vivo* magnetic hyperthermia treatment in a mouse. Magnetic nanoparticles were directly injected into the tumour of a mouse and an AC magnetic field was applied. D, Nude mice xenografted with cancer cells (U87MG) before treatment (upper row, dotted circle) and 18 days after treatment (lower row) with untreated control, $CoFe_2O_4$@$MnFe_2O_4$ hyperthermia, Feridex hyperthermia and doxorubicin, respectively. The same amounts (75 mg) of nanoparticles and doxorubicin were injected into the tumour (tumour volume, 100 mm^3,n=3). (with permission from Lee et al., 2011)

D). Due to the high surface-to-volume ratio in the nanoscale materials, surface-anisotropy becomes an important contribution to the total effective anisotropy. The 18 nm $Zn_{0.4}Fe_{2.6}O_4$ nanocube has a smaller surface anisotropy (K_s=1.6×10^{-5} J m^{-2}) compared to the 22 nm $Zn_{0.4}Fe_{2.6}O_4$ nanosphere (K_s=2.6×10^{-5} J m^{-2}), indicating the cube has a higher M_s (165 emu g^{-1}(Fe+Zn)) than that of the sphere. The high M_s will lead to a high SLP value (Noh et al., 2012).

In addition, the innovative vortex-domain structure has also been approved as an effective approach to largely improve the heat conversion efficiency of the magnetic nanoparticles. The Fe_3O_4 nanorings (Figure 6A and B) with uniquely appealing ferrimagnetic vortex-domain features show negligible remanence and coercivity (Figure 6C) that can greatly reduce dipole-dipole interactions and enable a good colloidal stability. Other features of these nanorings are a much higher saturation magnetization and a larger hysteresis loop in comparison with SPIOs. The SAR value of the FVIOs is as high as 3000 W g^{-1}. After magnetic hyperthermia treatment, the tumors were completely eliminated without recurrence within the experimental period (Figure 6E and F), indicating the FVIOs can be used as a promising hyperthermia therapeutic agent for cancer thermotherapy (Liu et al., 2015).

In general, heat can be transmitted through convection, radiation and conduction. It was observed that high heating power in aqueous suspensions may not translate into efficient heating in the cellular environment (Soukup et al., 2015). In the steady state of tumor, characterized by the balance between cell division and cell death, heat is depleted into the surrounding tissue by heat conduction and convection. In an ideal system, heat loss by convection is negligible compared with the heat transferred by conduction (Hergt and Dutz, 2007). Recently, it was discovered that decreasing the thickness of surface coating for improving thermal conductivity of magnetic nanoparticles is an important way to enhance the SAR (Liu et al., 2012).

In addition to magnetic hyperthermia, magnetic nanoparticles were also studied for photothermal therapy (Chu et al., 2013; Shen et al., 2013; Shen et al., 2015). Photothermal therapy (PTT) is an emerging, activatable, photo-based treatment which has attracted intensive interest in the field of biomedical research recently (Liu et al., 2007; O'Neal et al., 2004). Due to the fact that the NIR region (approximately

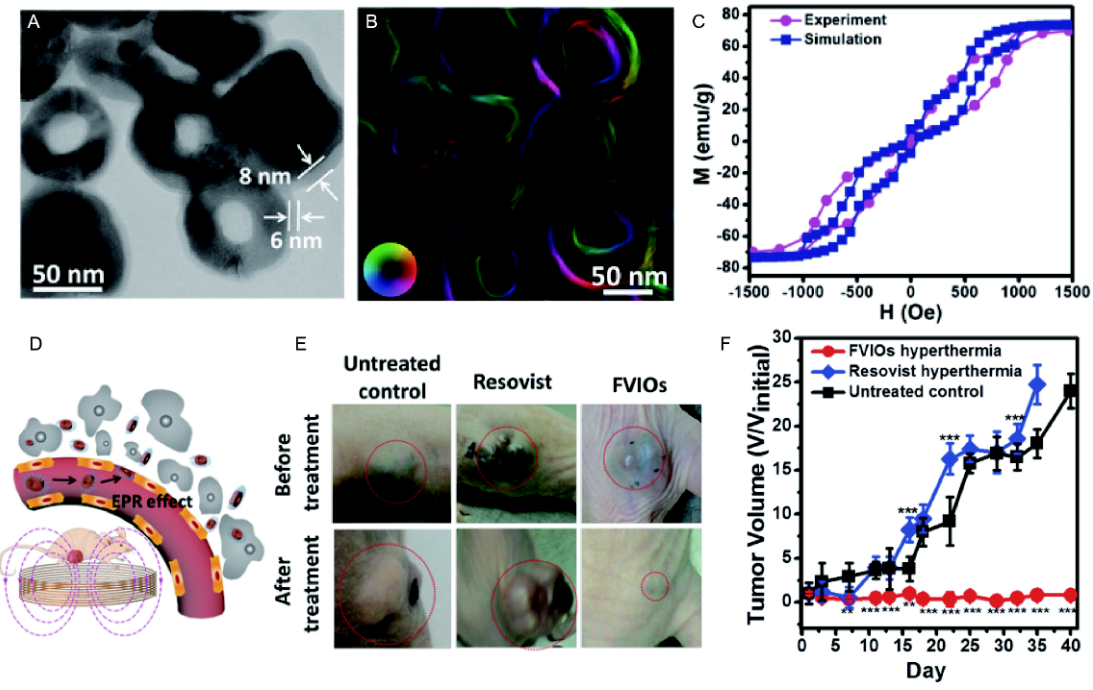

Figure 6 Ferrimagnetic vortex-domain iron oxide nanoparticle as a promising hyperthermia therapeutic agent. A, TEM image of FVIOs dyed with ruthenium tetroxide (RuO_4) in order to obtain a sufficient contrast for surface coating mPEG layer. B, Lorentz TEM image of FVIOs. C, Graph showing experimental and calculated average hysteresis loops for FVIOs. D, Schematics showing the effect of magnetic hyperthermia treatment on tumor cells in a mouse model. Magnetic nanoparticles were directly injected into the tumor of a mouse and an AC magnetic field was applied. E, Nude mice xenografted with breast cancer cells (MCF-7) before treatment (upper row, dotted circle) and 40 days after treatment (lower row) with untreated control, Resovist hyperthermia and FVIOs hyperthermia, respectively. F, Plot of tumor volume ($V/V_{initial}$) versus days after treatment with FVIOs hyperthermia, Resovist hyperthermia, and untreated control. (with permission from Liu et al., 2015)

700–900 nm) is above the endogenous chromophores adsorption and blow the water absorption, PTT under these wavelengths could maximize the treatment efficacy while minimize the degree of heat-destroyed normal tissues compared with other laser region (Huang et al., 2006). Magnetic iron oxide nanoparticles can display the NIR absorption which enables the transformation of NIR irradiation to heat for PTT. Compared with the conventional PTT agents (gold nanomaterials, carbon based nanomaterials, semiconductor nanoparticles, upconversion nanoparticles, NIR organic dyes and polymers) (Kumar et al., 2016; Tao et al., 2017; Yang et al., 2010), magnetic nanoparticles exhibit great potential as photothermal agent for clinical applications due to their low toxicity, high thermal stability and easy degradation.

One of the main challenges in PTT is the poor radiation-to-heat conversion efficacy with the NIR-sensitive NPs. There are many pertinent researches to solve the problem. Huang et al. reported that ligand-induced surface effect can promote a larger transition and a stronger NIR absorption of Fe_3O_4 nanoparticles (Liao et al., 2012). You et al. synthesized a series of monodispersed Fe_3O_4 nanoparticles with the size from 60 to 310 nm and systematically investigated their biobehavior and application. The 310 nm sized Fe_3O_4 nanoparticles generate the highest tumor temperature (55.3± 2.4°C) because these nanoparticles exhibit the highest amount of tumor retention, resulting in more efficient inhibition of tumor growth (Guo et al., 2016) (Figure 7A and B). Shi et al. investigated three formulations of iron oxide nanoparticles with different shapes (spherical, hexagonal and wire-like shapes). However, there are no obvious differences in photothermal effects among these nanoparticles (Chu et al., 2013). It was observed that the Fe_3O_4 nanoparticles can be used as both magnetic and photothermal agents. When the alternating magnetic field and near-infrared laser irradiation are applied simultaneously, the iron oxide nanocubes show a 2- to 5-fold higher heating effect than that of magnetic hyperthermia alone, yielding unprecedented heating powers (specific loss powers) up to 5000 W g^{-1}. For treatment of solid tumors, single-mode magnetic or photo hyperthermia treatment can reduce tumor growth, while DUAL-mode treatment results in complete tumor regression (Espinosa et al., 2016) (Figure 7C and D). Kim et al. reported a novel method to enhance the cytotoxicity of magnetic nanoparticles by selectively targeting a thermally susceptible subcellular organelle (i.e., mitochondria) (Figure 7E). The selective delivery of photothermal nanoparticles to subcellular organelle can realize a higher photothermal therapeutic efficacy in cancer treatment with minimal side effects. This study may open a new direction in the development of photothermal therapeutics (Jung et al., 2015).

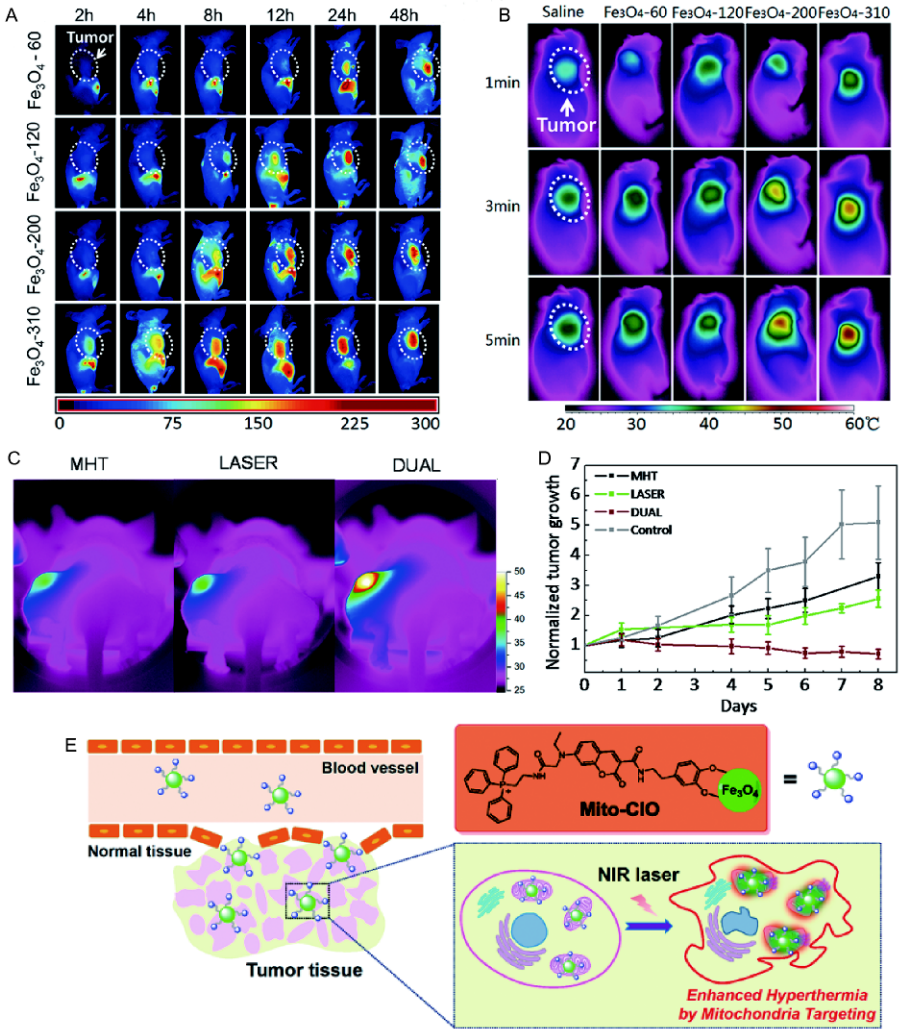

Figure 7 Magnetic nanoparticle as photothermal therapeutic agents. A, Whole body and tumor fluorescence images in tumor-bearing mice after intravenous injection of 200 μL of indocyanine green-labeled Fe_3O_4 nanoparticles at a concentration of 5 mg mL^{-1} Fe_3O_4. B, Thermographs of tumor-bearing mice that received photothermal treatment for different periods of time (with permission from Guo et al., 2016). C, Thermal images obtained with the IR camera in mice, after intratumoral injection of nanocubes (50 μL at [Fe]=250 mmol L^{-1}), in the left-hand tumor, and after 10 min application of magnetic hyperthermia (MHT, 110 kHz, 12 mT), NIR-laser irradiation (LASER, 808 nm at 0.3 W cm^{-2}), or DUAL (both effects). D, Average tumor growth (groups of six tumors each in non-injected mice submitted to no treatment (control) and in nanocube-injected mice exposed to MHT, LASER, and DUAL during the 8 days following the 3 days of treatment (with permission from Espinosa et al., 2016). E, Schematic representation of enhanced hyperthermia by using mitochondria-targeting iron oxide nanoparticles (with permission from Jung et al., 2015).

Current results in improving the radiation-to-heat conversion efficacy using magnetic nanomaterials have achieved a great success, but the development of magnetic nanoparticles-based new approaches and methodologies to further optimize the heat conversion efficacy is still imperative.

COMBINATION THERAPY

Much research has demonstrated that hyperthermia can make cancer cells more sensitive to ionizing radiation and chemotherapeutic agents. Hence, magnet mediated hyperthermia combined with either radiation or systemic chemotherapy could achieve synergistic anti-tumor effect and rapidly become a clinical reality for treating malignancy.

Thermo-radiotherapy

The cellular radiosensitivity could be remarkably enhanced after hyperthermia treatment. Strong evidence has proved that the mechanism of radiosensitization by heat is via interfering with processes at the chromosomal level and enhancing irreparable chromosome damages in comparison with that of irradiation alone (Kampinga et al., 2004; Kampinga and Dikomey, 2001; Horsman and Overgaard, 2007). Based on this, evaluation of the therapeutic effect of the combination of both radiation and magnetic hyperthermia modalities has been one of the most active research areas. For example, Gautam et al. proposed a self-regulating thermobrachytherapy seed, which serves as a source of both

radiation and magnetic hyperthermia for concurrent administration of thermo-radiotherapy. It showed a synergistic enhancement when both radiation and magnetic hyperthermia modalities are applied simultaneously (Gautam et al., 2012). Ivkov et al. reported a tremendous therapeutic effect by combining magnetic hyperthermia and radiation therapy using ^{111}In-chimeric L6 (ChL6) monoclonal antibody (mAb)-linked iron oxide nanoparticle in athymic mice bearing human breast cancer HBT 3477 xenografts. Furthermore, thermo-radiotherapy has been carried out in clinical trials (DeNardo et al., 2005). Phase II clinical trials of patients with glioblastoma, carried out by Jordan et al., demonstrated that tumors were completely eliminated without recurrence due to the synergistic enhancement antitumor effects of thermotherapy and radiation, and the survival period of patients has been extended to 13.4 months, an over 2-fold increase as compared to that of conventional radiation therapy alone (6.2 months) (Hauff et al., 2011).

Thermo-chemo therapy

Studies have showed that the inhibition of cancer cell growth after application of chemotherapeutic drugs, at elevated temperatures, was enhanced both in vitro and in animal experiments, indicating hyperthermia can effectively enhance the cytotoxicity of various anti-tumor agents (thermal chemosensitization) (Hervault and Thanh, 2014). The results of clinical trials strengthen the current evidence that hyperthermia combined with chemotherapy is an effective and practical modality for the cancer treatment. For example, in phase-III clinical trials, improved survival rates have been observed after adding local/regional hyperthermia to chemotherapy for patients with locally advanced or recurrent superficial and pelvic tumors (van der Zee, 2002; Wust et al., 2002). Plank et al. reported folate-targeted doxorubicin containing magnetic liposomes (MagFolDox) for thermo-chemotherapy. The combined magnetic and folate receptor targeting increased the accumulation of MagFolDox in cancer cells and magnetic hyperthermia at 42.5°C and 43.5°C synergistically increased the cytotoxicity of MagFolDox (Pradhan et al., 2011). Toshinobu Yogo et al. reported a smart ferrofluid contained Fe_3O_4 nanoparticles, alginate, cysteine and anticancer drug (i.e., doxorubicin, DOX) can transform immediately into a gel in tumors. When the AMF is applied, the generation of magnetic hyperthermia by Fe_3O_4 can heat the gels, resulting in gel shrinkage and DOX release for the combination of magnetic hyperthermia and chemotherapy (Hayashi et al., 2016).

In a word, although further detailed investigations are still necessary, tentative use of drug-loaded magnetic nanocomposite in local tumor therapies, which aims to achieve more specific chemotherapeutic release in combination with magnetic hyperthermia, is promising and feasible in the long term.

IMMUNOTHERAPY AND CELL THERAPY

Different types of cancer immunotherapies including cytokine therapy, checkpoint-blockade therapy, adoptive T-cell transfer especially the emerging chimeric antigen receptor T (CAR-T) cell therapy, as well as cancer vaccines, have demonstrated some exciting clinical responses. Among these immunotherapies, cancer vaccines may own some unique advantages including induction antigen-specific immunities against tumors and long-term immune-memory effect (Chen et al., 2016). Vaccination strategies which involve dendritic cells (DCs) have been developed owing to the special properties of these cells in coordinating innate and adaptive immune responses (Palucka and Banchereau, 2012). Dendritic cells (DCs) are antigen-presenting cells with a unique ability to induce primary immune responses. DCs are not only critical for the induction of primary immune responses, but may also be important for the induction of immunological tolerance, as well as for the regulation of the type of T cell-mediated immune response (Banchereau et al., 2000). It is important to use magnetic nanoparticles in DC-based immunotherapy. Because the magnetic nanoparticles can offer exceptional contrast and provide high-resolution *in vivo* images with good signal-to-noise ratios for tracking DC migration via magnetic resonance imaging (MRI). On the other hand, the generation of heat in an alternating magnetic field (AMF) of magnetic nanoparticles could induce antitumor immunity (Yanase et al., 1998). Seong et al. reported an iron oxide-zinc oxide core-shell nanoparticle for carrying carcinoembryonic antigen into dendritic cells. The iron oxide nanoparticles are used to detection of nanoparticle-labeled DCs by MRI. Mice immunized with dendritic cells containing the nanoparticle-antigen complex showed enhanced tumor antigen specific T-cell responses, delayed tumor growth and better survival than controls (Cho et al., 2011). The immunotherapy is often used in combination with magnetic hyperthermia. For example, Kobayashi et al. examined the feasibility of combined hyperthermia and immunotherapy for malignant melanoma. Magnetite cationic liposomes (MCLs) were injected into a B16 melanoma nodule in C57BL/6 mice for magnetic hyperthermia treatment. After 24 h, granulocyte macrophage-colony stimulating factor (GM-CSF), which plays an important role in the activation of antigen-presenting cells, was injected directly into the melanoma. This is the first time that the combination of local injection of MCLs and GM-CSF, which has been shown to exhibit an obvious antitumor effect against malignant melanoma (Ito et al., 2003).

Cell-based therapy holds great promise for the treatment of human disease. Development of cell-based therapy requires tracking the *in vivo* fate and distribution of transplanted cells to maximize the therapeutic efficacy. Recently, superparamagnetic iron oxide (SPIO) nanoparticles appear to be

the most applicable probe to cell therapy. Huang et al. reported that the labeling human mesenchymal stem cells (hMSCs) with ferucarbotran (FDA-approved iron oxide nanoparticle) can induce epidermal growth factor receptor (EGFR) overexpression in hMSCs, which can be attracted by tumorous epidermal growth factor (EGF) and more effectively migrated toward tumor than unlabeled cells. The overexpressed EGFR of ferucarbotran-labeled hMSCs can bind the tumorous EGF by blocked EGF/EGFR signaling-derived tumor growth, tumorous angiogenesis, and tumorous VEGF expression, which are also responsible for tumor progression and development, resulting in more potent intrinsic antitumor activity (Chung et al., 2011). Another work shows that label macrophages with SPIO for treatment of orthotopic primary and metastatic (lung) prostate tumors. When the pulsed magnetic field gradients in the direction of the tumor sites is applied, magnetic field guides SPIO-loaded macrophages from the bloodstream into tumors, resulting in increased tumor macrophage infiltration and reduction in tumor burden and metastasis (Muthana et al., 2015).

THERANOSTICS

"Theranostics" was first proposed in 1998 by John Funkhouser, the Chief Executive Officer of PharmaNetics, as a concept of "the ability to affect therapy or treatment of a disease state". As a treatment strategy, theranostics includes personalized medicine, pharmacogenomics, and molecular imaging. It aims to monitor the response to the treatment, improve drug efficacy and safety and eliminate unnecessary treatment of patients to save cost for the overall healthcare system (Lim et al., 2014). The "nanotheranostics" is usually understood as the combination of therapeutic and diagnostic functions within a single nanoparticle, which uses diagnosis to aid or guide nanoparticle therapy procedures so as to solve clinical issues and improve treatment outcomes (Chen et al., 2017; Ho et al., 2011; Yoo et al., 2011). The magnetic nanoparticles have shown great advantages as a promising paradigm for cancer nanotheranostics, because it can play multiple roles as both MR imaging probe and hyperthermia therapeutic agent simultaneously. These characteristics facilitate magnetic nanoparticles to construct high-performance theranostic nanoplatform for imaging guided cancer therapy.

Molecular imaging is an important component for theranostics. The magnetic nanoparticles can be used as T_2 contrast agent for detection of cancer. Gao et al. prepared the biocompatible magnetite nanoparticles via one-pot reaction. Then, the Fe_3O_4 nanocrystals were conjugated with a cancer-targeting antibody for *in vivo* T_2 MRI detection of tumor (Li et al., 2005; Hu et al., 2006). The T_2 contrast ability can be optimized by tuning size, composition, shape and surface modification. Cheon et al. investigated the size effect of Fe_3O_4 nanoparticles for T_2 MRI (Jun et al., 2005) and then conjugated Fe_3O_4 with herceptin for *in vivo* monitoring of human cancer cells implanted in live mice (Huh et al., 2005). He also investigated the composition effect of the Fe_3O_4 nanoparticles based MRI T_2 contrast agent by doping Fe_3O_4 using Mn, Co and Ni. The $MnFe_2O_4$ showed the strongest MR contrast effect. After conjugating $MnFe_2O_4$ with cancer-targeting antibody herceptin, the high MR sensitivity of $MnFe_2O_4$-herceptin conjugates enables the MR detection of tumors (Lee et al., 2007).

However, intrinsic dark signal in T_2-weighted MRI can be easily confused by the other hypointense areas such as bleeding, calcification, or metal deposition, misleading clinical diagnosis. Moreover, the "blooming effect" induced by high magnetic moment of T_2 contrast agents can blur the image (Na and Hyeon, 2009). Thus, further optimization of the contrast agents to afford T_1 contrast ability is required for ultrasensitive imaging of biological targets, early diagnosis of cancer and monitoring the process of cancer treatment. Recent progress in the magnetic nanoparticles based MRI contrast agent mainly focuses on the ultrasmall (less than 5 nm) iron oxide nanoparticles. Hyeon et al. synthesized on a large scale extremely small-sized iron oxide nanoparticles (ESIONs) with the size less than 4 nm. The ESIONs can be used as T_1 blood pool MRI contrast agent for detecting the myocardial infarction, renal failure, atherosclerotic plaque, thrombosis, and angiogenesis of tumor cells (Kim et al., 2011). He then used the extremely small iron oxide nanocluster to do the preclinical evaluation in MRI of large animals (Lu et al., 2017). Fan et al. proposed a dynamic simultaneous thermal decomposition method for synthesis of the ultrasmall metal ferrite nanoparticles. The as-prepared $MnFe_2O_4$ nanoparticles can be used as multifunctional blood-pool and liver-specific T_1 MRI contrast agent (Zhang et al., 2017) (Figure 8A).

The magnetic nanoparticles also can be used to monitor the cancer treatment. Different magnetic nanoparticles based theranostic platforms are developed. For example, Fan et al. have reported ferromagnetic $Fe_{0.6}Mn_{0.4}O$ nanoflowers (FIMO-NFs) as a new class of magnetic theranostic platform for *in vivo* T_1-T_2 dual-mode magnetic resonance imaging and magnetic hyperthermia therapy. The mouse orthotopic glioma are clearly delineated in both T_1- and T_2-weighted MR images, after administration of the FIMO-NFs. The encapsulation/loading of magnetic nanoparticles and drugs within a carrier is another important component for theranostic platform (Liu et al., 2016). Lecommandoux et al. reported the maghemite nanoparticles and doxorubicin were encapsulated within block copolymer vesicles for MR imaging and magneto-chemotherapy. The maghemite nanoparticles acted as imaging agent in MRI and magnetic hyperthermia induced controlled drug release (Sanson et al.,

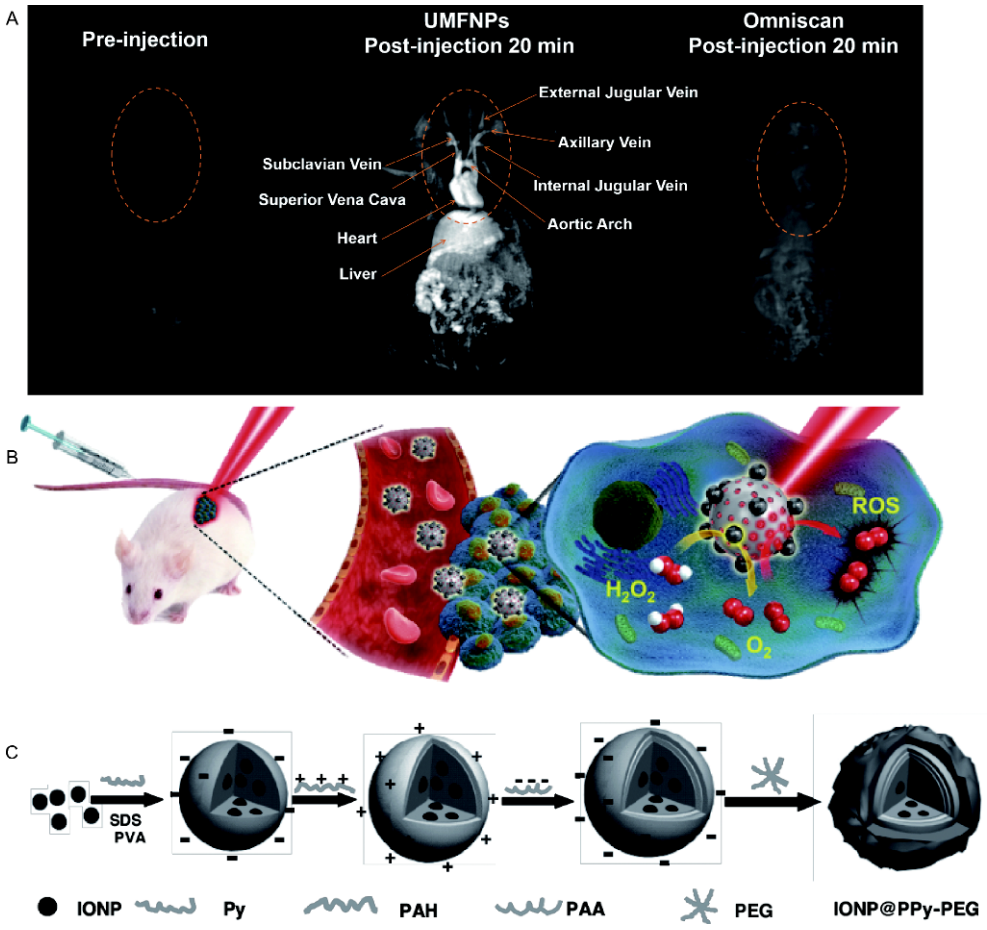

Figure 8 (Color online) Magnetic nanoparticle as theranostic nanoplatform. A, *In vivo* ultrasmall $MnFe_2O_4$ nanoparticles enhanced MR images (with permission from Fan et al., 2017). B, Schematic illustration of MFMSNs (with permission from Kim et al., 2017). C, Schematic showing the fabrication process of IONP@PPy-PEG nanocomposite (with permission from Song et al., 2014).

2011). Hyeon et al. reported manganese ferrite nanoparticle-anchored mesoporous silica nanoparticles (MFMSNs) to overcome hypoxia and enhance the therapeutic efficiency of photodynamic therapy. The $MnFe_2O_4$ nanoparticles can be used to continuously produce O_2 via the Fenton reaction in a H_2O_2-rich cancer microenvironment, and also exhibit T_2 contrast effect in magnetic resonance imaging (MRI), allowing for *in vivo* tracking of MFMSNs (Kim et al., 2017) (Figure 8B). In addition, the magnetic nanoparticles also can be used as a carrier to load agent for imaging guided cancer treatment. Perez et al. reported modified solvent diffusion method for the co-encapsulation of both an anticancer drug and near-infrared dyes on the iron oxide nanoparticles. The obtained theranostic nanoparticles could allow combined optical/magnetic resonance imaging and targeted cancer therapy (Santra et al., 2009). Liu et al. reported a method to coat ultrasmall iron oxide nanoparticles (IONP) with a NIR-absorbing conjugate polymer (polypyrrole, PPy), resulting in IONP@PPy nanocomposite. The nanocomposite is then modified with the biocompatible polyethylene glycol (PEG) through a layer-by-layer method to acquire high stability (Figure 8C). The as-obtained IONP@PPy-PEG show multimodal magnetic resonance and photoacoustic imaging guided photothermal therapy (Song et al., 2014). Wu et al. developed a multifunctional theranostic platform using exceedingly small magnetic iron oxide nanoparticles for T_1-weighted MRI and chemotherapy (Shen et al., 2017).

CONCLUSION

In summary, we have reviewed the current status of magnetic nanoparticles and their applications in cancer therapy including intrinsic therapeutic effect, therapeutic delivery, hyperthermia treatment, combination therapy and thernostics. The design and construction of high-performance magnetic nanoparticles-based anti-cancer agent for cancer treatment have been discussed. The advantages and fundamentals of magnetic nanoparticles should be given increasing attention to extend potential therapeutic function of magnetic nanoparticles. Much effort in cancer nanomedicine has been devoted to improving the therapeutic efficacy using magnetic nanoparticles, but safer and more effective cancer therapies that make full use of nanoscale features of mag-

netic nanoparticles are still far from being accomplished. We expect that the magnetic nanoparticles based cancer therapy will make significant progress to clinical translation via multidisciplinary research approach and fulfill the goal of prolonging patient survival in the clinics in the near future.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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