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SPECIAL ISSUE: Biomaterial Foundations of Therapeutic Delivery

Magnetic drug delivery systems

Yang Liu, Mingxi Li, Fang Yang* and Ning Gu*

ABSTRACT **There has been unprecedented progress in the development of biomedical nanotechnology and nanomaterials over the past few decades, and nanoparticle-based drug delivery systems (DDSs) have great potential for clinical applications. Among these, magnetic drug delivery systems (MDDSs) based on magnetic nanoparticles (MNPs) are attracting increasing attention owing to their favorable biocompatibility and excellent multifunctional loading capability. MDDSs primarily have a solid core of superparamagnetic maghemite (γ-Fe_2O_3) or magnetite (Fe_3O_4) nanoparticles ranging in size from 10 to 100 nm. Their surface can be functionalized by organic and/or inorganic modification. Further conjugation with targeting ligands, drug loading, and MNP assembly can provide complex magnetic delivery systems with improved targeting efficacy and reduced toxicity. Owing to their sensitive response to external magnetic fields, MNPs and their assemblies have been developed as novel smart delivery systems. In this review, we first summarize the basic physicochemical and magnetic properties of desirable MDDSs that fulfill the requirements for specific clinical applications. Secondly, we discuss the surface modifications and functionalization issues that arise when designing elaborate MDDSs for future clinical uses. Finally, we highlight recent progress in the design and fabrication of MNPs, magnetic assemblies, and magnetic microbubbles and liposomes as MDDSs for cancer diagnosis and therapy. Recently, researchers have focused on enhanced targeting efficacy and theranostics by applying step-by-step sequential treatment, and by magnetically modulating dosing regimens, which are the current challenges for clinical applications.**

Keywords: magnetic nanoparticles, magnetic assembly, drug delivery system, multimodality, theranostics

INTRODUCTION

Magnetic nanoparticles (MNPs), based on iron, cobalt, nickel, or metal oxides, have attracted significant attention owing to their intrinsic magnetic properties, which allow them to be tracked by magnetic resonance imaging (MRI) [1–4]. However, in the past few decades, the focus of laboratory researchers has shifted from pure material synthesis and characterization to the design of more comprehensive but practical therapeutic delivery systems. In recent years, integrated medical material for both diagnosis and simultaneous treatment has also become very attractive for doctors and patients because it can save a great deal of time and money. Based on this requirement, MNPs, previously used as a powerful diagnostic tool, are being considered as theranostic delivery systems combining imaging agents and effective therapeutic drugs [5–9].

Precise control parameters are pivotal in the synthesis and surface functionalization of MNPs because they determine the physicochemical properties, colloidal stability, and biological behavior and/or fate of the magnetic drug delivery systems (MDDSs). There is a large variety of MNPs, but superparamagnetic iron oxide nanoparticles (SPIO NPs) such as magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) have great potential in nanomedicine. SPIO NPs have been widely utilized owing to their biocompatibility and "superparamagnetism". When exposed to an external magnetic field, they immediately reach saturation magnetization. When the external magnetic field is removed, they are demagnetized and do not retain any magnetism. SPIO NPs can be precisely directed to targeted tissue *in vivo* by exploiting their rapid response to external magnetic fields [10–15]. For specific pharmaceutical and biomedical purposes, MNPs should be modified by the incorporation of appropriate molecules on their surfaces. Owing to the large surface area of nanomaterials and their activated functional surface groups, it is very convenient to anchor a targeting agent to the MNP surface. Moreover, the number of targeting molecules can be readily controlled. For

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example, biocompatible polymers such as polyethylene glycol (PEG) can be linked to the surface of MNPs to provide "stealth" properties while avoiding clearance by the reticuloendothelial system (RES). Target proteins such as herceptin can be conjugated on the surface of MNPs to facilitate their active delivery to breast tumors [15–18]. The design and fabrication of elaborate and advanced MNP-based DDSs is a promising approach to controlled loading and accurate multistep delivery [19].

MNPs are currently used in nanomedicine in different ways. For example, cancer chemotherapy requires the administration of high doses of cytotoxic drugs owing to their lack of specificity, which may lead to severe cytotoxic effects [20]. To avoid such side effects, MDDSs could be designed as smart drug delivery nanosystems to transport an effective drug dosage and specifically target tumor cells. The *in vivo* behavior of the drug could be further controlled by localizing it at the lesion site using an external magnetic field. Followed the application of another appropriate stimulation, the loaded drugs/imaging agents can be released locally [21–24]. In this review, we will summarize recent progress in the design and fabrication of multifunctional MDDSs for biomedical applications. After a brief introduction to the basic physicochemical and magnetic properties that are desirable for MDDSs, we will discuss the surface modification and functionalization issues that arise when designing elaborate MDDSs for future clinical applications. Finally, we will survey recent progress in the design and fabrication of controllable MNPs, magnetic assemblies, and magnetic microbubbles and liposomes for use in multimodal imaging and targeted drug delivery.

PHYSICOCHEMICAL PROPERTIES OF MAGNETIC NANOPARTICLES FOR DRUG DELIVERY SYSTEMS

To better serve *in vivo* applications, researchers have designed a series of MNPs with different combinations of cores and surface modifications. Firstly, it is necessary to have an overall understanding of how the physicochemical characteristics of MNPs affect their stability, pharmacokinetics, biodistribution, endocytotic pathway, and biotoxicity. By characterizing how geometry, hydrodynamic size, surface features, magnetism, and biotoxicity influence the delivery process (Fig. 1), researchers are able to redesign MDDSs with optimum therapeutic effects.

Hydrodynamic size and geometry

To achieve optimum efficacy, therapeutic agents must reach sufficient doses to kill tumor cells, but at the same time, they should not adversely affect normal tissues. MNPs with large volumes or surface areas could carry sufficient drug molecules while avoiding clearance by RES. Therefore, shape and size must be carefully considered and optimized because they affect drug release and pharmacokinetics *in vivo* [25–27].

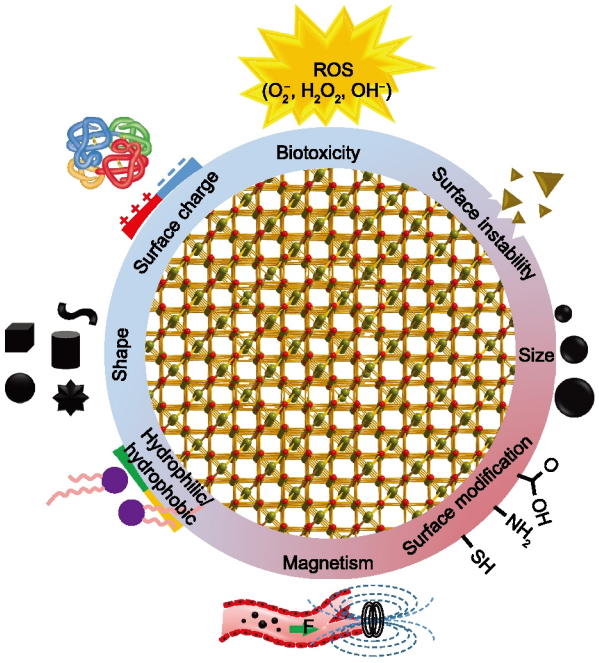

Figure 1 Physicochemical considerations of MNPs for drug delivery systems.

Circulation in the blood and extravasation of nanoparticles require the design of rational complex nanostructures *in vivo*. Small nanoparticles (<5 nm) might be rapidly removed from vessels by renal clearance or liver uptake, whereas large nanoparticles (>200 nm) are removed by the spleen or the RES [28,29]. Therefore, nanoparticles between 20 and 200 nm can be kept in blood circulation because they can escape from the body's scavengers [30]. Longer blood circulation time and higher plasma concentration ensure that nanoparticles can penetrate the epithelial cells in the vicinity of tumors and accumulate at a higher concentration at the targets. Furthermore, MNP drug delivery vehicles for theranostics, combined imaging, and hyperthermia treatment are also dependent on the magnetic properties of MNPs. Thus, the size of the MNPs should be carefully considered when designing MDDSs for *in vivo* applications.

Apart from the influence of MNP size, studies have shown that the shape of the nanoparticles may dictate the cellular fate of internalized MNPs [25]. Although few

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studies have focused on non-spherical nanoparticles to date, research has proved the plausibility of this speculation. Inhibition of phagocytosis by controlling shape succeeds by minimizing regions of high length-normalized curvature on the particles. Champion *et al.* [31] presented the idea that particle geometry can be used to modulate the phagocytosis of drug delivery particles, and demonstrated a significant reduction in particle uptake that was solely due to particle geometry. Worm-shaped nanoparticles, in particular, meet this criterion and have the potential to significantly affect drug delivery by avoiding phagocytosis compared with traditional spherical particles. Cheng *et al.* [32] demonstrated that the difference between uptakes of spherical MNPs and rod-shaped MNPs by HeLa cells might also be attributed to their morphological effects. Furthermore, MNPs with a high aspect ratio (from 100:1 to 500:1) have also been evaluated *in vivo*. The results revealed that constructs with a molecular weight of approximately 350–500 kDa were rapidly (half life, $t_{1/2} \sim 6$ min) cleared intact by glomerular filtration; these constructs were much bigger than the molecular weight cutoff for glomerular filtration (30–50 kDa). Although the *in vivo* bio-behaviors of non-spherical MNPs may not be as predictable as we imagined, these observations have allowed the design of novel nanoscale-based shaped structures with unusual pharmacologic and pharmacokinetic characteristics [29].

Surface features

Once MNPs, which are distinct antigenic substances, are injected into the blood stream, and before they contact cells, they are recognized by the body's immune system. Their movement and release are affected by various cells and proteins in the blood. The MNP surface charge is regarded as one of the essential factors that directly relates to the cellular uptake of MNPs [23,33–35]. A surface charge is generated when most of the solid surface contacts water, an aqueous solution, or another highly polar liquid [36]. Owing to Coulombic force, the charged surface attracts solute ions of the opposite electric charge, resulting in the accumulation of high concentrations of counter ions at the interface. The Stern model postulates that a closely adsorbed ion layer, called the Stern layer, forms at the surface, and an outer layer, called the diffuse layer, also forms in which attraction decreases as distance increases. The potential of this double layer is called the zeta potential (ζ), and is a critical factor for the *in vitro* and *in vivo* stability of the MNPs. The zeta potential can be calculated indirectly by electrophoresis, photon correlation spectroscopy (PCS), and electroacoustic methods. In the macroscopic system, the effect of the surface charge between the solid-liquid interface is usually less significant and is neglected. However, under the micro-/nanosystem, the surface charge may have a critical effect on the behavior of the interface and the stability of colloidal particles. Understanding the structure of the electric double layer, and the effect of the surface charge on the interface of MNPs, will help us to more precisely control the surface charge to achieve the properties demanded by a specific application [37].

The surface charge of MNPs depends on the material coating them. For example, MNPs with a high number of amine groups are expected to have a positive charge, whereas hydroxyl and carboxyl groups usually confer a negative charge. Theoretically, because MNPs directly contact the charged head groups of proteins on the cell surfaces, positively charged MNPs are endocytosed by cells more easily, because the electronic potential of the cell membrane is negative. The experimental results produced by many researchers have proved this view. Yang *et al.* [38] determined that there was a greater concentration of positively charged (aminopropyltrimethoxysilane (APTMS)-coated) MNPs inside cells than negatively charged (bare or tetraethyl orthosilicate (TEOS)-coated) MNPs. In particular, large numbers of APTMS-coated MNPs widely adhered to the immediate vicinity of the cell membrane, and several particles even translocated to the cell nucleus. Sun *et al.* [39] demonstrated that with a similar concentration, positively charged aminosilane-coated iron oxide nanoparticles (AmS-IONPs) reduced the viability of neurons by 50%, whereas negatively charged COOH-AmS-SPIOs reduced viability by only 20%. Toxicity appears to be dependent on the surface coating as opposed to the amount of iron oxide present in the cell. However, there is still some dissent among researchers regarding the zeta potential on the MNPs. Prijic *et al.* [40] proved that the cellular uptake of anionic silica-coated MNPs was three-fold greater than that of cationic-modified nanoparticles. Negative citrate groups increase the stability of MNPs and improve their affinity for the cell membrane. These contradictory experimental results illustrate the complex identification and phagocytosis process that occurs between cells and MNPs, in which surface charge is only one of many influencing factors.

Magnetism

As a DDS, MNPs should be capable of accumulating in selected regions to avoid adversely affecting the surrounding or non-targeted normal tissues. Therefore, MNPs are designed to have specific affinity for targeted regions through external guidance or internal stimuli. One of the most

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common ways of accomplishing this is to utilize the magnetic properties of the MNPs. Because the magnetic moments of the atoms of ferromagnetic materials are non-zero, each atom acts like a tiny permanent magnet. When the atoms are clustered into a small region, and the magnetic moments are evenly arranged in parallel, the small region is called the magnetic domain [41]. The existence of magnetic domains is a consequence of minimizing energy. Assuming that a ferromagnetic bulk comprises multiple magnetic domains, the magnetic fields of the magnetic domains are different and cancel each other out, resulting in a zero-sum vector. Because the magnetic moment of the whole object is zero, it cannot attract other magnetic materials. However, if the ferromagnetic material is exposed to an external magnetic field, the magnetic domain starts to move. If the direction of the magnetic domain is approximately the same as the direction of the external magnetic field, the magnetic domain expands; if the directions are different, it contracts. At this point, if the magnetic field is switched off, the magnetic domain may not return to the original unmagnetized state. Therefore, when the ferromagnets are small enough, the nanoparticles randomly change direction owing to thermal perturbation. When there is no external magnetic field, they usually do not exhibit magnetic properties. However, once an external magnetic field is applied, the MNPs become magnetized, a phenomenon known as superparamagnetism [42].

In the absence of an external magnetic field, superparamagnetic materials do not retain residual magnetism; this property could be exploited to avoid the tendency to agglomerate in colloidal dispersions [43]. In fact, researchers have demonstrated that reduced intrinsic ferromagnetism ensures non-toxicity under physiological conditions. Furthermore, driven by external magnetic fields, MDDSs can provide controllable movement, accumulation, and release within the organism [44]. For instance, some researchers have found that magnetic composites can be localized upon the application of an external magnetic field and can circumvent the human skin barrier, and even penetrate deep subcutaneous tissue *via* follicular pathways [20].

Moreover, by responding to an external alternating magnetic field, MNPs can convert dissipated magnetic energy into thermal energy. Thus, it is envisaged that MNPs will be used for hyperthermia treatment of cancer or hyperthermia-controlled drug release [13,45–47]. MNPs generate heat under an alternating magnetic field as a result of various pathways strongly correlated with their morphological, structural, and magnetic profiles. As shown in previous studies [48], magnetic hyperthermia efficiency may be enhanced by controlling the core-shell morphology of mixed ferrites compared with their single-phase counterparts. More thorough research is required in order to obtain better energy conversion efficacy.

Biotoxicity

When MNPs are engineered for use as biomedical DDSs, their toxicity has also been a concern. As prerequisites for clinical application, complete knowledge of the toxicological properties and a risk assessment of the MNPs are mandatory to ensure safety and minimize potential health hazards.

At present, MDDSs are commonly designed with a core of magnetic nanomaterials and a shell of polymer materials or other inorganic metal compounds. Methods for *in vivo* detection of MNPs are mainly based on the determination of iron content using elemental analysis of collected blood [49]. However, because most biomedical MNPs are iron-based [50], the quantitative determination of the iron content to obtain an understanding of the pharmacokinetics of the MNPs is complicated by the presence of endogenous iron. However, some new technologies such as alternating current magnetic susceptibility measurements facilitate differentiation between the endogenous iron present in the tissues in the form of ferritin and the iron storage protein from MNPs [51]. Ruiz *et al*. [51] demonstrated that *meso*-2,3-dimercaptosuccinic acid (DMSA)-coated iron oxide nanoparticles are safe for biomedical applications. They administered the nanoparticles to rats at dose levels of 2.5, 7.5, and 15 mg Fe/kg body weight and monitored their body weight, food consumption, gross pathology, and the bio-distribution of iron in their spleens and livers. Many studies have compared the toxicity of different magnetic nanomaterials during cell coculture [52–56]. Park *et al*. [55] proved that after the cells were exposed to 50 μg mL^{-1} of bare magnetite and maghemite for 24 h, Fe_3O_4 decreased cell viability to 11.0 ± 1.0 % of the control level. Adenosine monophosphate (ATP) production decreased to 9.5 ± 0.6 % of the control level. The levels of reactive oxygen species, nitric oxide, and pro-inflammatory cytokines were elevated. Damage to the mitochondria and the endoplasmic reticulum, and downregulation of mitochondrial function and transcription-related genes were also higher in the cells. However, although γ-Fe_2O_3 produced the same results, the degree of the effect was lower.

Therefore, to reduce toxicity, the iron core is generally coated with biocompatible materials such as dextran, DMSA, PEG, or polystyrene [57–59], which will be de-

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scribed in detail in the next section. Researchers even hope to use biocompatible modifications to avoid unnecessary tissue aggregation and cell endocytosis, thereby ensuring the biosafety of the MDDS. For example, dextran-stabilized MNPs do not induce oxidative stress-mediated toxicological effects, nor do they alter physiological processes or behaviors, or visible pathological lesions [60]. Peeples *et al*. [61] showed that coating Fe_3O_4 nanoparticles with (3-aminopropyl) triethoxysilane and citric acid caused no significant decrease in cell viability up to 25 μg mL^{-1} compared with uncoated Fe_3O_4 when incubated with lung epithelial cells (RL 65-Rat source). The experimental analysis of the effects of DMSA-modified MNPs on higher concentrations and longer incubation times also showed that DMSA-MNPs have little toxicity in this cell line. There is no notable influence on cell proliferation. It was further proved that treatment with various concentrations of DMSA-MNPs led to an insignificant decrease in glutathione (GSH) levels [62]. These results confirm the potential of surface coated MNPs for clinical use.

In addition to directly designing iron nanoparticles as drug carriers, the magnetic responsive capability of MNPs is often used to affect drug release under external magnetic field stimulation. Therefore, a combination of MNPs with static magnetic field (SMF), or alternating magnetic field may cause potential negative effects for clinical applications. Unfortunately, there are very few reports on this problem. Bae *et al*. [63] reported that under conditions that satisfied the conventional cytotoxicity assessment of 0.5 mmol L^{-1} SPIO, clinical doses combined with 0.4T SMF exposure exert synergistic adverse effects such as reduced cell viability, apoptosis, and cell cycle aberrations on hepatocytes *in vitro* and *in vivo*. Moreover, long-term monitoring showed a significant increase in multinuclear giant cells in the cells concomitantly treated with SPIO and SMF compared with the control. Therefore, further studies on the molecular mechanisms underlying cellular responses to both MNPs and magnetic field interactions are necessary for a comprehensive assessment and a thorough understanding of the systemic effects on the living body.

SURFACE FUNCTIONALIZATION OF MAGNETIC NANOPARTICLES FOR *IN VIVO* TARGETING

To improve stability, reduce biotoxicity, and achieve extended circulation under physiological conditions, MNPs need to be functionalized by encapsulating a variety of inorganic or organic materials such as polymers, lipids, and proteins, or further conjugating functional moieties to their coatings such as targeting ligands, therapeutic peptides/antibodies, fluorescent dyes, or gene agents. Table 1 summarizes common organic and inorganic surface modifications for better *in vivo* results. The surface modifications can provide protection for the magnetic core, preventing aggregation by screening the magnetic dipolar attraction between the MNPs. They ensure an ideal magnetic platform for further drug loading and retain chemical inertness with normal tissues in biological systems.

Organic coating materials

Polymer coating materials

Improving the targeting efficiency of MNPs while reducing their negative impact *in vivo* has always been a challenge for MDDS applications. To solve this problem, MNPs for *in vivo* use require a coating that: (1) reduces MNP aggregation; (2) extends the circulation time of the MNPs *in vivo*; (3) avoids nonspecific intercellular interactions and reduces cytotoxicity; and (4) provides a platform for the conjugation of drugs and targeting molecules. To achieve these coating functions, various polymers including PEG, poly(ethyleneimine) (PEI), chitosan, polylactic acid (PLA), and dextran have been investigated.

PEG has several advantages, such as low toxicity, no antigenicity, good amphiphilicity and biocompatibility, and thus has been used clinically as an excipient in Food and Drug Administration (FDA)-approved pharmaceutical formulations [74]. PEG-coated (or PEGylated) MNPs can usually avoid recognition by the RES, thereby improving the biocompatibility of MNPs. PEG can be further combined with certain proteins, targeting ligands, or therapeutic agents. Even by covalently binding to the other end of PEG, such magnetic complexes can achieve both efficient surface coating and multi-functionalization. Yuan *et al*. [75] prepared well-defined PEGylated MNPs (PEG-Fe_3O_4) with excellent dispersibility and dissolvability under physiological conditions for the photothermal therapy of cancer cells *via* a facile one-pot solvothermal method. Various hybrid MNPs coated with PEG or carboxylated PEG [76], such as PEGylated iron oxide-gold core-shell nanoparticles [77], combine a variety of specific ligands for applications in diagnostic magnetic particle imaging (MPI) [78], MRI [79], and the treatment of many diseases.

Chitosan, which is a partially acetylated glucosamine (poly(1→4)-2-amino-2-deoxy-d-glucan) [80], was firstly synthesized in 1859. This natural polymer has bio-functionality, biodegradability, biocompatibility, bioactivity, and other excellent properties, and has attracted attention

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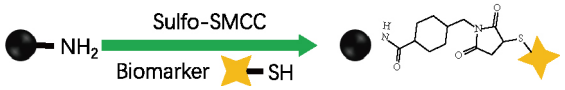
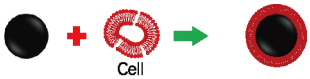
Table 1 Materials used to modify the surface of MNPs for *in vivo* applications

	Modification method	Materials	Illustration	Reference
Organic materials	End-grafted	PEG		[18]
	Surface adsorption	Chitosan		[64]
		Dextran		[65]
		PEI		[66]
		PVP		[67]
	Conjugation	$-NH_2$		[38]
		–SH		[68]
		–COOH		[69]
	Biomimicry	RBC membrane		[70]
		PLT membrane		[71]
Inorganic materials	Conjugation	Au		[72]
		Ag		[73]
		Si		[70]

Note: PEG = polyethylene glycol; PEI = poly(ethyleneimine); PVP = polyvinylpyrrolidone; RBC = red blood cell; PLT = platelets.

in the fields of chemistry and biology. Chitosan-coated MNPs contain a core of magnetic material, usually a mixture of Fe_3O_4 and γ-Fe_2O_3 [81], or hybrid MNPs (nickel-ferrite) [82], with the drug loaded on the surface for targeted, controlled release. Dorniani *et al.* [83] designed a new drug nanocarrier by coating chitosan and perindopril erbumine on the surface of MNPs using a simple coating method. Such chitosan-modified MDDSs have minimal toxicity. In addition, chitosan has reactive groups such as –OH and $-NH_2$, which can be used for further integration of MNPs with targeting, imaging, and therapeutic agents.

PEI is a hydrophilic cationic polymer with high affinity for DNA, proteins, and cells [84]. It is often used in conjunction with PEG for coating MNPs to enhance colloidal stability and reduce biotoxicity. Schweiger *et al.* [85] developed a novel magnetic carrier system based on the assembly of PEG-PEI and MNPs to develop γ-Fe_2O_3 PEG-PEI particle systems. Such nanodelivery systems have good long-term colloidal stability and low toxicity in the presence of PEG groups on the polymer backbone, and have great potential for biomedical applications.

Dextran is a water-soluble polysaccharide that is mainly composed of α-d-(1→6)-linked glucose units with some α-d-(1→3)-linked units [57]. As a natural polysaccharide, dextran is widely used in the pharmaceutical field and has attracted much attention [86]. It has a strong affinity for the hydroxyl groups on the surface of MNPs. Dextran-modified MNPs can increase the half-life of the drug under physiological conditions. Many dextran-coated MNPs have been prepared for use as MRI contrast agents and targeted drug delivery carriers because they have good biocompatibility [58,59,87,88]. Dextran can also be coated on hybrid MNPs. The dextran-coated gold MNPs synthesized by Li *et al.* [89] had enhanced colloidal stability and could be used for the controlled release of doxorubicin (DOX).

A variety of other polymers or copolymers are also used for the encapsulation of MNPs, including polyvinyl alcohol (PVA) [90,91], polylactic acid/poly(lactic-co-glycolic acid) (PLA/PLGA) [92], and polyvinylpyrrolidone (PVP) [93–96]. These polymers have different properties and can influence the properties of MNPs, such as the surface

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charge, function, dispersibility, and magnetic properties, in different ways. Modified MNPs can successfully endure the aggregation of particles under physiological conditions and retain a good crystalline structure and magnetic properties, which make them ideal for controlled drug delivery in tumor therapy.

Bioconjugation coating materials

Coating strategies using polymers such as PEG and PLA to improve the surface properties of MNPs have been highly successful at solving the biocompatibility problem. The further bioconjugation of functional structures on the surface of MNPs has been reported to enhance targeting capability. Wang *et al*. [97] designed (3-aminopropyl)triethoxysilane-modified FeCo MNPs, which were subsequently activated by glutaraldehyde, leading to the successful bioconjugation of proteins (streptavidin, pregnancy-associated plasma protein A antibody, and nectin-4 antibody) with the aldehyde groups on the nanoparticle surfaces. Protein-FeCo conjugates have much higher saturation magnetization than commercially available iron oxide nanoparticles. In addition, some protein drugs/genes can also be used to modify the surface of MNPs to achieve the targeted delivery of biological drugs. Yang *et al*. [98] developed low-toxicity magnetic nanocarriers with a shell of poly(aniline-co-*N*-(1-one-butyric acid) aniline) over a Fe_3O_4 MNP core to carry recombinant tissue plasminogen activator (rtPA) for targeted thrombolysis treatment.

Natural biological coating materials

The modulation of immunocompatibility by the chemical modifications described above is limited owing to exogenous toxicity. Recent studies on the immunological response of artificial material-modified nanoparticles have prompted researchers to pursue alternatives. A cell membrane-based top-down nanoparticle modification strategy has proved successful. Rao *et al*. [99] made use of natural red blood cell (RBC) membranes to camouflage the surface of Fe_3O_4 nanoparticles for reducing RES uptake. The combination of MNPs and natural cell membranes embodies a biomimetic nanocoating strategy for designing new biological magnetic nanomaterials. Owing to their self-recognition function, autologous cells that mimic the MDDS strategy have a great advantage in biomedical applications. Mimicking MNPs with other types of autologous cell membranes such as those of leukocytes, platelets, cancer cells, hepatocytes, and stem cells is a current research hot spot.

Inorganic coating materials

Owing to the combination of the magnetic core and the functionalized shell, hybrid MNPs with a core-shell structure have a wide range of applications [100,101]. Many inorganic materials such as SiO_2, or precious metals such as gold, silver, or platinum, are used for the nuclei or shells of MNPs. These coated hybrid MNPs have enhanced stability, improved biocompatibility, and surface chemical, biological, or catalytic interfacial reactivity.

Silica-coated MNPs

Recently, core-shell structured silica/MNP composites have been studied extensively [102–104]. Silica-coated MNPs can be used for MRI imaging and hyperthermia treatment. The preparation of silica-coated MNPs with good physical and chemical properties is a prerequisite for subsequent use. Rho *et al*. [105] described a facile two-step method for synthesizing monodispersed, silica-coated MNPs. Oleate-MNPs were successfully converted to polyvinylpyrrolidone-MNPs (PVP-MNPs), which were then coated with silica using a modified version of the Stöber method. More than 95% of the MNPs were individually coated with a silica shell without non-magnetic core silica nanoparticles, which were stable for more than three months. Studies on silica-coated MNPs indicate that these particles have the potential for use in biomedical applications. Owing to the presence of MNP cores, silica-coated MNPs can be used for hyperthermia treatment. Iqbal *et al*. [102] prepared silica-coated manganese ferrite nanoparticles for hyperthermia applications. Silica-coated manganese ferrite nanoparticles can be used to heat aqueous solutions to 42°C, and are therefore useful for magnetic hyperthermia treatment. Compared with research into organic coating materials such as PEG, PEI, and lipids, there has been little research into silica as an inorganic coating material for MNPs until recently. Silica-coated MNPs may be useful in various biomedical fields such as diagnostics and therapeutic treatments because they are biocompatible, stable, non-toxic, easily functionalized, and have excellent magnetic properties.

Gold-coated MNPs

Gold (Au)-coated MNPs with a core-shell structure can be used for MRI, magnetically targeted drug delivery, surface-enhanced Raman scattering (SERS), and catalysis. Owing to their unique properties, gold-coated magnetic composites can be used for both diagnosis and therapeutics. Shen *et al*. [106] recently reported the design of gold-coated Fe_3O_4 nanoparticles. The nanoparticles were functionalized by the self-assembly of a single layer of azide groups on the surface, which could be conjugated with folate molecules *via* copper (I)-catalyzed azide-alkyne

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cycloaddition. The experimental results showed that the nanoparticles could be used for the non-immunogenic targeting of cancer cells. Owing to the multifunctional modification of Au-coated MNPs, multimodal imaging and photothermal therapy can be envisaged in the future. In addition to Fe_3O_4, the core of gold-coated MNPs can be synthesized from other hybrid materials. Poudyal *et al.* [107] reported a novel method for preparing a FePtAu core-shell structure using solution phase chemistry combined with solvothermal annealing, which showed great promise for various optical, sensing, and biomedical applications. Wang *et al.* [108] designed Au-coated $MnFe_2O_4$ nanoparticles, which were first modified with a uniform PEI layer (2 nm). The negatively charged Au seeds were then adsorbed onto the surface of the $MnFe_2O_4$ nanoparticles *via* electrostatic interaction during the formation of the Au shell. Synthetic Au-coated hybrid MNPs have useful properties such as strong magnetic response, good SERS activity, enhanced stability, and biofunctionalization. Moreover, the thickness of the gold layer can be varied as required to achieve different properties, making the nanoparticles potentially useful for a broad range of applications in diagnosis and therapeutics.

Silver-coated MNPs

When silver (Ag) is combined with MNPs, silver-MNP composites with both optical and magnetic properties are obtained. The biocompatibility of the nanoparticles can be improved. Chen *et al.* [109] reported the one-pot synthesis of Ag-Fe_2O_3 hybrid nanoparticles by the sequential addition of precursor chemicals. It is possible to adjust the hybrid structure from a core-shell to a heteromeric geometry by changing the reaction temperature. Owing to the slow diffusion of silver ions out of the Fe_2O_3 shell, the hybrid material has an enhanced magnetic-targeting, bactericidal function. Zhai *et al.* [27] were the first to describe a solvothermal method whereby Fe_3O_4 grains were distributed directly onto the surface of Ag seeds. They constructed Ag-Fe_3O_4 hybrid MNPs with a core-shell structure, which had both plasmonic and significant superparamagnetic properties. Silver-iron hybrid MNPs can also be synthesized by the *in situ* reaction of precursor chemicals. Bian *et al.* [110] prepared monodispersed Ag/polyaniline/Fe_3O_4 nanoparticles with an average size of approximately 50 nm *via in situ* reduction between emeraldine PANI/Fe_3O_4 and silver nitrate. Magnetite-silver hybrid nanoparticles can easily be tuned to a core-shell or heteromer structure [25], and show great potential for application in the fields of tumor treatment using magnetic hyperthermia, SERS, antibacterial applications, and optical imaging.

MAGNETIC NANOPARTICLES AND ASSEMBLED COMPOSITES AS DRUG DELIVERY SYSTEMS FOR THERANOSTICS

The inability of traditional drug delivery carriers to specifically accumulate at the target site and escape the biological barriers reduces drug efficiency and stability, and can even lead to serious side-effects. Therefore, the use of biocompatible carriers to carry therapeutic drugs with improved pharmacokinetic properties has attracted the attention of researchers. MNP-assembled MDDSs have been regarded as an attractive alternative for delivering drugs owing to their low toxicity, biocompatibility, and controllable release characteristics. Although it is well known that MNPs can be used as MRI contrast agents for tumor imaging, recent multifunctional MDDSs have extended the potential uses of MNPs by combining multimodal imaging with targeted drug delivery; the MNPs can be loaded with radiotherapy, chemotherapy, anti-inflammatory, or anticancer drugs.

Magnetic nanoparticles themselves as a drug delivery system

In the early stages of MNP development, researchers regarded MNPs as chemically inert materials, and they have mainly been used as MRI contrast-enhancing agents and spontaneous DDSs. However, subsequent studies have revealed that MNPs have pH-dependent peroxidase and catalase activities like those of certain enzymes. Chen *et al.* [111,112] reported that iron oxide nanoparticles can catalyze H_2O_2 to produce the hydroxyl radical (·OH) under acidic conditions, and the hydroxyl radical is then able to oxidize a variety of organic molecules. That is, the MNPs have peroxidase-like activity. Under neutral conditions, iron oxide nanoparticles directly catalyze the degradation of hydrogen peroxide into H_2O and O_2 (Fig. 2); that is, they have hydrogen peroxidase-like enzyme activity. Such pH-dependent enzyme activity of MNPs has prompted new lines of investigation into the use of MNPs themselves as "drugs" for the treatment of disease.

An attempt has been made to exploit the enzymatic activities of MNPs to treat certain diseases. Xiong *et al.* [113] reported the preparation of the DMSA-coated Fe_2O_3 MNPs (Fe_2O_3@DMSA), which have a spherical core with an average diameter of 9.8 nm, using a coprecipitation method. Importantly, Fe_2O_3@DMSA showed the potential for drug-like activity, preventing cardiac arrest in a rat coronary artery ligature model. The size of the myocardial infarction and the biochemical indices further demon-

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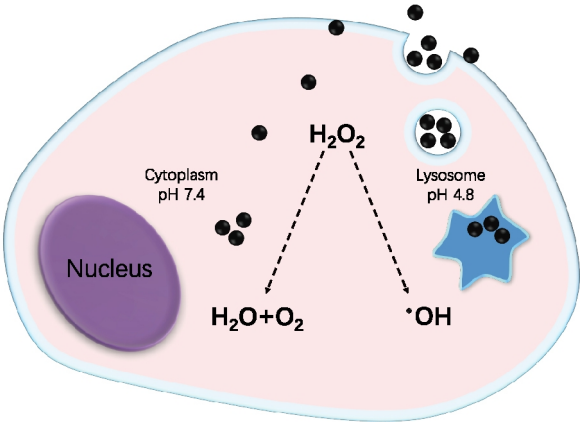

Figure 2 Schematic illustration of peroxidase- and hydrogen peroxidase-like enzyme activities of iron oxide nanoparticles, modified from reference [111], Copyright 2012, American Chemical Society.

strated that Fe_2O_3@DMSA nanoparticles can successfully protect the myocardium from ischemia injury in animals. Further, it is found that the MIM, a multifunctional scaffold protein to regulate both actin dynamics and membrane dynamics, may play a positive role in the MNPs uptake process. Therefore, the silence of MIM is important for avoiding the endocytosis process of MNPs by RAW 264.7, which may enhance the MNPs accumulation in target sites [114].

The discovery of the mimetic enzyme activity of MNPs has prompted researchers to explore new strategies for their synthesis, laying the foundation for further MNP applications. There have been some reports that naturally occurring ferritin is equivalent to a storage compartment for iron in animal and plant cells [115]. Zhang *et al.* [116] devised a strategy to use ferritin as a template for the synthesis of small, Prussian blue-modified ferritin nanoparticles (PB-Ft NPs), which retain the biological characteristics of ferritin. Their results showed that the PB-Ft NPs have a mean size of 22.8 nm, and retain specificity and peroxidase-like activity. Therefore, PB-Ft NPs can be used as biocatalytic and biometric tools. However, contrary to widespread speculation, the electron spin resonance test results show that PB-Ft NPs cannot catalyze H_2O_2 to produce ·OH. On the contrary, PB-Ft NPs clean up harmful ·OH, which indicates that PB-Ft NPs do not act as peroxidases through the Fenton reaction. Further experimental results reported by Zhang *et al.* [117] show that PB-Ft NPs exert a catalytic function through a charge transfer mechanism. Moreover, PB-Ft NPs can effectively quench O_2 and H_2O_2 in several cell models, i.e., PB-Ft NPs act as nanoscale reactive oxygen species (ROS) scavengers that effectively relieve ROS-induced cell damage. However, the detailed cellular mechanism underlying this property of PB-Ft NPs is unclear and requires further investigation. Moreover, Yang *et al.* [118] have developed a new strategy of ultrasound and MR dual modal imaging, which has a complementary advantage that enables simultaneous treatment and multimodal monitoring based on PB-Ft NPs. PB-Ft NPs are able to catalyze the decomposition of H_2O_2 into oxygen (O_2) molecules at neutral pH (pH 7.4). This chemical reaction produces an O_2 bubble-forming molecule that can be used as an ultrasound contrast agent to enhance ultrasound imaging. Thus, PB-NPs provide a multi-functional nanoscale platform; they can be used for dual-mode imaging and as scavengers to reduce oxidative stress *in vivo*.

The results mentioned above suggest that the biological activity of MNPs may be very complex. Some researchers have reported that MNPs have enzymatic activity that resembles the effects of certain drugs, and can also promote the osteogenic differentiation of human bone marrow mesenchymal stem cells (hBMSCs) to modulate stem cell fate for promoting tissue repair [119,120]. Wang *et al.* [121] analyzed the gene expression of hBMSCs that had been incubated with MNPs at an appropriate concentration using a gene chip assay and bioinformatics analysis. They found that the classical mitogen-activated protein kinase (MAPK) signaling pathway was activated by NPs. Thus, the downstream gene of the pathway is regulated to promote osteogenic differentiation. This study elucidates the molecular basis of how MNPs affect hBMSCs, which may have significant implications for stem cell applications in regenerative medicine.

Magnetic nanoparticle assembly as a drug delivery system

Employing MNPs as a DDS is another common use of MNPs. MNPs are able to transport anticancer drugs into tumor cells without damaging healthy cells. Compared with other nanodrug delivery systems such as polymer nanoparticles, liposomes, and micelles, MDDSs have better MRI performance, which may make it possible to dynamically monitor the drug distribution *in vivo*. Furthermore, MNPs are biodegradable, which greatly benefits their biomedical applicability. However, the efficacy of the MNPs as drug nanocarriers is often counteracted by the rapid conditioning and subsequent plasma clearance of the tissue macrophages of the RES before the nanoparticles reach the target tissue or cell [122]. Although we have developed many ways of loading MNPs with drugs, magnetic carriers may perform poorly when a large drug release

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at the target area is required. Smaller particles provide a larger surface area and are therefore more suitable for drug loading, but this comes at the expense of reduced magnetic properties. To solve this problem, Xiong *et al.* [123] assembled four separate oleic acid-terminated iron oxide nanotubes and oleic acid-modified PEG molecules to form clusters (Fig. 3). These nanomagnetic clusters maintained high paclitaxel (PTX) drug loading, high magnetism, and rapid and extended release behavior. Compared with the same dose of free PTX, the PTX magnetic nanoassemblies had greater antitumor activity *in vivo*. Simultaneously, with the increase of tumor cell uptake, the magnetic nanoassemblies provided tumor imaging by MRI. Benefiting from the high drug loading capacity and high magnetic characteristics, such magnetic nanoassembled DDSs can maximize the advantages of nanomaterials and minimize their side-effects.

Moreover, biodegradable and biocompatible polymer-assembled MNP structures have been fabricated based on their controlled drug release characteristics, and have been used in biomedical imaging, cell labeling, and therapy [124]. Yang *et al.* [125] found that MNP-embedded PLA exhibited controlled drug release that was dependent on the MNP assembly concentration in the polymer. PLA-MNP material with a concentration of 20% MNPs in the composite increased the drug release rate by more than 200 times while maintaining excellent controlled drug release. It was also found that the interaction between MNPs and various crystal PLA domains on the surface of the PLA-nanoparticle composites affected the behavior of the PLA during hydrolysis.

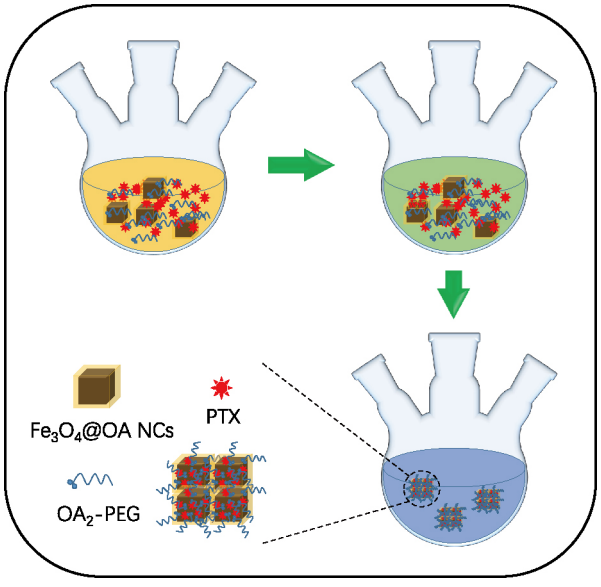

Figure 3 Schematic representation and structure of Rubik's cube-like PTX magnetic nanoassemblies, modified from reference [119], Copyright 2016, Elsevier.

Magnetic microbubbles and liposomes as multimodality theranostic delivery systems

Apart from the direct use of MNPs as a drug adsorption platform for *in vivo* delivery, many authors have reported microcapsule structures that encapsulate MNPs in organic or inorganic shells [126], where the microcapsules act as an effective platform for the simultaneous delivery of encapsulated drugs and MNPs. Drugs or other biologically active substances can be embedded in the internal area of the microcapsules, thereby preventing the drugs from contacting healthy tissue before reaching the disease site or the specific tissue. The shell structure of the microcapsules is then changed by the application of an external magnetic field and/or physiological microenvironment triggers. This triggers the release of the drug from the microcapsules. The structure could be called a "smart" magnetic nanodevice owing to the precision by which the drug release is achieved to optimal effect. Yang *et al.* [127] designed a micro-container embedded with Fe_3O_4 nanoparticles. Nitric oxide precursor drugs and l-arginine were also encapsulated in the core of the micro-container. Under the stimulation of an alternating magnetic field, the permeability of microcapsule membrane was changed, and H_2O_2, which commonly resides in the inflammatory region, is released into the interior resulting in a bubble microreactor formation *in situ*. The reaction, product nitrogen oxide (NO), is beneficial because it alleviates tissue inflammation and acts as an ultrasound contrast agent to monitor targeted tissue with ultrasound imaging. Thus, the magnetic field-triggered NO microbubbles can be utilized like a very simple, but important and effective magnetic nanodevice to achieve the diagnostic and therapeutic goal.

Subsequently, further experiments were designed to investigate the use of magnetic microbubbles with therapeutic capabilities. After binding to tumor-targeted biomolecules, the magnetic microbubbles can be developed as molecularly targeted imaging DDSs. In one experiment, arginine-glycine-aspartic acid-L-tumor necrosis factor-related apoptosis-inducing ligand (RGD-L-TRAIL), an antitumor-targeting fusion protein, was precisely conjugated to the surface of the MNP-coated microbubbles to construct RGD molecularly targeted magnetic microbubbles (RGD-L-TRAIL@MMBs) [128]. Owing to the highly specific accumulation of RGD-L-TRAIL@MMBs in the tumor, accurate diagnostic information about the tumor

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can be obtained by dual ultrasound and MRI (Fig. 4). After imaging, the TRAIL molecules act as anticancer agents and gain access to the interior of the cancer cells by nanoparticle- and RGD-mediated endocytosis to effectively induce tumor cell apoptosis. It is expected that a proper MNP-based microbubble DDS could be developed as a molecularly targeted multimodality imaging delivery system with the addition of chemotherapeutic cargoes to improve cancer diagnosis and therapy.

Finally, taking into account the superior biocompatibility of liposomes, magnetic liposomes are also frequently developed and applied. Liposomes are artificial phospholipid vesicles with a mean diameter of 50–1000 nm. Both water-soluble and water-insoluble drugs/nanoparticles can be loaded into the inner core and hydrophobic bilayer, respectively, forming a promising DDS [129]. When the hydrophobic or hydrophilic MNPs are loaded into the liposome formulation, the fabricated magnetic liposome delivery systems can be remotely controlled *via* an external magnetic field. Traditionally, magnetic liposomes make excellent MR contrast agents. In particular, the MR of magnetic liposomes simultaneously facilitates image guidance of the liposomal drug delivery in the specific areas *in vivo*. An innovative class of magnetic hyperthermia and smart controllable liposomes have been developed. Sharifabad *et al.* [130] prepared liposome-capped core-shell mesoporous silica-coated SPIOs called "magnetic protocells" as novel nanocomposites, and used them for loading the anticancer drug DOX. The structure was adjusted to maintain a temperature of 43°C with a concentration of 10 mg mL^{-1} in a variable magnetic field with a maximum strength of 200 Gauss and a frequency of 406 kHz. A slow but linear increase in DOX release over time at 43°C was demonstrated to be favorable for drug delivery applications without affecting the structure of the capped liposomes. Liu *et al.* [131] designed a stimuli-responsive anethole dithiolethione (ADT)-loaded magnetic nanoliposome (AML) delivery system, which consists of ADT and a hydrogen sulfide (H_2S) pro-drug doped in the lipid bilayer, and superparamagnetic nanoparticles encapsulated inside. For *in vivo* applications, after preferentially targeting the tumor tissue when spatiotemporally navigated by an external magnetic field, the nanoscale AMLs can intratumorally convert to micro-sized H_2S bubbles. This dynamic process can be monitored by magnetic resonance and ultrasound dual modal imaging. Importantly, the intratumoral-generated H_2S bubbles visualized by real-time ultrasound imaging can first ablate the tumor tissue when exposed to higher acoustic intensity; then as gasotransmitters, intratumoral-generated high-concentration H_2S molecules can diffuse into the inner tumor regions where they have a further synergistic antitumor effect. The 7-day follow-up observations for tumor-bearing mice indicated that AMLs and magnetic field treatment greatly improved the inhibition of tumor growth.

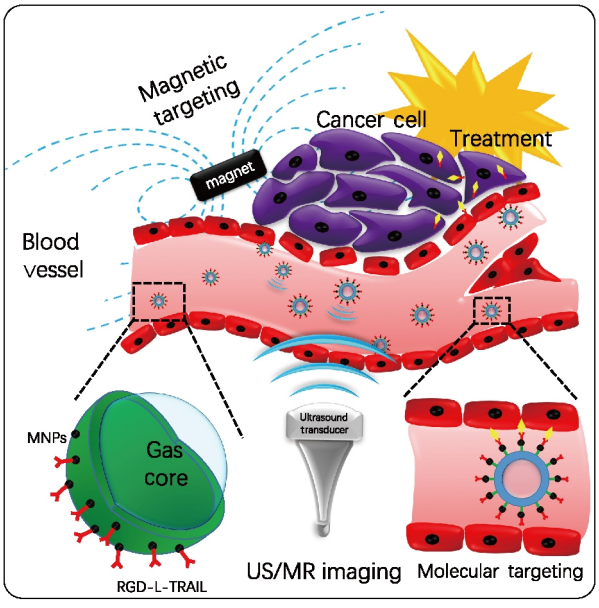

Figure 4 Schematic diagram showing the enhanced targeting strategy of RGD-L-TRAIL@MMBs for tumor diagnostics and therapy.

Very recently, a cell membrane-mimicking lipid composition presented as a novel surface mask for MNPs has been shown to confer various biological benefits. It is reported that platelet (PLT) membrane-coated Fe_3O_4 MNPs, which may inherit prolonged blood circulation and cancer targeting capabilities from the PLT membranes, are a tentative design for personal therapy [71]. The T_2-weighted relaxation rate value (R_2) of the PLT-MNPs suggests that the surface membrane coating does not compromise MRI functionality. The *in vivo* MRI images confirmed that the PLT-MNPs have better tumor accumulation behavior than uncoated MNPs. Tumor photothermal therapy with PLT-MNPs exhibited tumor temperature increases from 34.4 to 56.1°C within 5 min. In contrast, the tumor temperatures of MNP and RBC-MNP groups in mice reached only 49.5 and 53.6°C, respectively.

CONCLUSIONS

MNPs have emerged as excellent multifunctional nanoplatforms for the construction of smart DDSs. Numerous designs have been made in this field over the last 10 years, reflecting an exponentially growing number of

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publications. A search of the Web of Science that stipulated "magnetic nanoparticles" and "drug delivery systems" as two keywords produced 805 hits, and the total cited frequency was 21,184 hits. Moreover, 81.86 % of the publications were original articles, 17.89% were reviews, and 4.48% were reports of proceedings, conference abstracts, and editorials. Furthermore, 27.70% of the publications were from the United States, 23.85% from China, and 6.83% from South Korea. The contributions from China are increasing sharply year on year.

With a gradual increase in clinical requirements, although most DDSs, including MNPs, are in mutually competitive development stages, MDDSs have become one of the most promising DDSs. MNPs with suitable physicochemical properties, modified with biocompatible polymeric, lipid, or metal shells, are applicable to a wide variety of biomedical fields, both diagnostic and therapeutic. As discussed, the size, charge, and surface features of MNPs could strongly influence their biodistribution, biotoxicity, and magnetism. Administrated MDDSs, utilizing external magnetic fields, can be transported to targeted diseased tissues, where the drugs can be released in a controllable manner. As a result of less drug cargo dosage and precise delivery, MDDSs do not exhibit serious side-effects. Even temperature increases arising from exposure to an alternating magnetic field have been investigated for tumor hyperthermia treatment. A number of positive *in vivo* results for MDDS suggest that work should progress from the laboratory to clinical trials.

However, before these MDDSs can be used commercially as diagnostic and therapeutic products, numerous challenges must be overcome. First, the *in vivo* metabolic processes in which these elaborate MDDSs are involved after injection are not very clear. To date, *in vivo* studies on the fate of iron are scarce, and macroscopic analysis of the quality distribution of MNPs in organs cannot explain the different mechanisms underlying specific cell phagocytosis, metabolism, degradation, and cell death. More emphasis should be put on detailed investigations of the *in vivo* properties of MNPs if these nanoparticles are to enter clinical trials. Continuing from this unsolved problem, more experimental data are needed for a comprehensive understanding of what happens to the MDDSs in the long term. The toxicity of the MNPs is complex and depends on their size, geometry, surface features, and magnetism. Thus, from a regulatory standpoint, the *in vivo* safety of MNPs needs to be evaluated more carefully. Furthermore, it is known that the functions of MDDSs and the property of external magnetic fields are inseparable. However, owing to the restrictions imposed by physical conditions and the differences between patients with different diseases, external magnetic fields should be carefully modulated for effective treatment. Until now, few studies have explored the influence of magnetic fields on MDDSs. Despite the numerous challenges faced when exploring specific favorable clinical applications, the *in vitro* and *in vivo* experimental results are encouraging. Any efforts that improve the properties of MDDSs *in vivo* and reduce their clinical cost will accelerate the development of magnetic theranostic delivery systems in the future.

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Conflict of interest The authors declare that they have no conflict of interest.

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基于磁性质的药物递送系统

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摘要 随着过去几十年来生物医学纳米技术和纳米材料领域的持续发展, 基于纳米颗粒的药物输送系统逐渐开始有望应用于临床研究. 其中, 由于具有良好的生物相容性和优异的多功能负载能力, 基于磁性纳米粒子的磁性药物传递系统受到越来越多的关注. 本综述首先总结了磁性药物传递系统的基本物理化学性质, 以阐明磁性药物传递系统需要保持适当的性能以满足特定的临床需要; 其次, 讨论了在设计未来临床应用的磁性药物传递系统时的表面修饰和功能化问题; 最后, 重点综述了磁性纳米颗粒、磁性组装体以及磁性微泡、磁性脂质体和生物膜修饰的磁性载体系统的设计和制备最新进展. 最后, 本综述对目前研究的磁性载体系统的设计、制备和安全性进行了总结, 并对未来进一步解决磁性药物传递系统的临床应用瓶颈和前景进行了展望.

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