Tzu Chi Medical Journal 2023; 35 (1): 11-17

Review Article

Diagnostic and therapeutic roles of iron oxide nanoparticles in biomedicine

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Abstract

Nanotechnology changed our understanding of physics and chemics and influenced the biomedical field. Iron oxide nanoparticles (IONs) are one of the first emerging biomedical applications of nanotechnology. The IONs are composed of iron oxide core exhibiting magnetism and coated with biocompatible molecules. The small size, strong magnetism, and biocompatibility of IONs facilitate the application of IONs in the medical imaging field. We listed several clinical available IONs including Resovist (Bayer Schering Pharma, Berlin, Germany) and Feridex intravenous (I.V.)/Endorem as magnetic resonance (MR) contrast agents for liver tumor detection. We also illustrated GastroMARK as a gastrointestinal contrast agent for MR imaging. Recently, IONs named Feraheme for treating iron-deficiency anemia have been approved by the Food and Drug Administration. Moreover, tumor ablation by IONs named NanoTherm has also been discussed. In addition to the clinical application, several potential biomedical applications of IONs including cancer-targeting capability by conjugating IONs with cancer-specific ligands, cell trafficking tools, or tumor ablation agents have also been discussed. With the growing awareness of nanotechnology, further application of IONs is still on the horizon that would shed light on biomedicine.

Keywords: *Iron oxide, Magnetic resonance imaging, Molecular imaging, Nanotechnology*

Submission : 23-Mar-2022
Revision : 03-May-2022
Acceptance : 08-Jun-2022
Web Publication : 27-Jul-2022

Introduction

Nanotechnology in biomedicine

Nanotechnology is defined as the synthesis and manipulation of materials between 1 and 100 nm [1]. Due to the proximity diameter of iron oxide nanoparticles (IONs) to atoms, these materials exhibit different physical and chemical properties than their corresponding bulk materials. For instance, as the diameter of gold is <30 nm, the color of these gold particles appears ruby red [2]. Furthermore, the surface area of nanomaterials is dramatically increased compared to its volume, making the chemical catalytic process quick. The abundance of the surface area is advantageous when the primary nanoparticles are conjugated with a small ligand, making the particle multifunctional. Nanotechnology-based liposomal drugs have been launched for anticancer efficacy. With different pharmacodynamic/pharmacokinetics of these liposomes compared to their small-molecule form, these liposomes have different anticancer indications [3]. The most famous one is Doxil® (Baxter International, USA), which is the liposomal form of doxorubicin. Unlike doxorubicin which has dose-related cardiotoxicity and myelosuppression, Doxil® has higher drug concentration in certain malignancies such as Kaposi's sarcoma and ovarian cancer [4,5].

IONs are one of the nanocomposites that enter the clinical field. Unlike liposomal drugs with small, active molecular components, IONs are composed of an iron oxide core with a hydrophilic coating. The paramagnetic iron oxide core plays an essential part in biomedical applications such as contrast medium for magnetic resonance imaging (MRI) or magnetic beads for specific cell sorting [6]. The scale comparison of IONs, liposomes, and the scale of natural materials is illustrated in Figure 1.

Physics and biochemical properties of iron oxide nanoparticles

IONs are magnetite ($FeO \cdot Fe_2O_3$) or maghemite (γ-Fe_2O_3) core [7,8]. The core is not water soluble. Therefore, coating with water-soluble polymers such as dextran, carboxydextran,

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_65_22

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How to cite this article: Lu CH, Hsiao JK. Diagnostic and therapeutic roles of iron oxide nanoparticles in biomedicine. Tzu Chi Med J 2023;35(1):11-7.

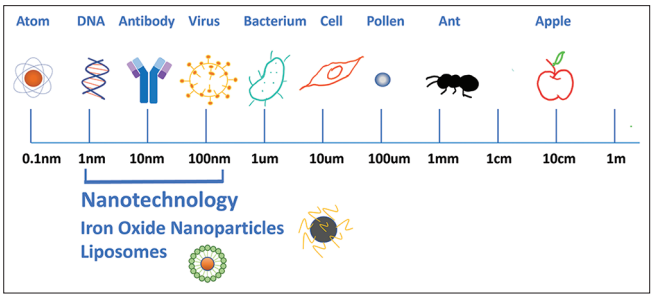

Figure 1: Scale comparison of Biomedical Nanomaterials and Natural Materials

or polyethylene glycol (PEG) is mandatory. A small molecule such as citrate or glutathione coating for the synthesis has also been tried [9,10]. Magnetite is the most magnetic natural mineral [11]. However, for the synthesis of nanosized iron oxide core, the bottom-up chemical synthesis methods are preferred over top-down physical methods [12]. Some biological techniques such as bacterial synthesis of IONs have also been tried [13]. The size of the iron oxide core is heavily dependent on the synthesis methods, which could also influence the magnetic properties. The selection of coating of iron oxide core is dependent on the purpose of the IONs. However, water-solubility, biocompatibility, and less immunogenicity are three of the necessities [14]. For most of the current clinical available I.V. MR contrast agent, IONs are coated with dextran (Feridex I.V./Endorem) or carboxydextran (Resovist), which could be metabolized by liver and kidneys. Attempts to coat iron oxide core with water-soluble silicates have been tried with successful clinical results such as GastroMARK [15,16]. Although silicates cannot be metabolized by liver and kidneys, oral ingestion is a safe delivery method. These silicate-coated IONs are currently available for gastrointestinal MR contrast medium, which could pass through gastrointestinal tract without retention in the body.

All of the IONs have magnetism. Under 10 nm, the iron oxide core is paramagnetic, which means that the magnetic property of the iron oxide core could reach the saturated magnetism exposed to a high magnetic field [17]. However, the magnetism of the iron oxide core could be reversed once if the polarity of the magnetic field has been reversed. Most importantly, the magnetism of the iron oxide core could return to zero when the surrounding magnetic field was removed [18]. The assurance of the paramagnetism of the iron oxide core could avoid hazardous clustering of IONs after exposure to a high magnetic field such as MRI [14]. According to the hysteresis loop study, Resovist has the coercive field (Hc) of zero and saturated magnetism of 80 emu/g [19].

Metabolization of iron oxide nanoparticles

The biological reaction and metabolization of IONs is dependent on the size, surface charge, and coating of the IONs. Consequently, these IONs are mostly located at the liver, where RES is abundant. For those IONs diameter <30 nm, the lymphatic system will recognize these IONs, and most of these IONs are accumulated in the lymph nodes or spleen. If the IONs are designed not to be recognized by immune cells, PEG coating is mostly used [20,21]. Strategies of PEG binding antibody drug are often used in the pharmaceutical industry to prolong the antibody drug circulation time in the blood stream [22]. The PEG conjugation of the IONs is significant if targeted molecular imaging is required [23]. Once RES takes up the IONs, the surface coating of the carbohydrates will be metabolized, whereas the iron oxide core is transformed into an iron storage pool to synthesize the hemoglobin [21]. Consequently, the IONs with either PEG or dextran/carboxydextran coating are completely biocompatible and could be metabolized as iron source or eliminated to bile or urine. As to the silicate-coating IONs, the delivery route is oral and could be passed into gastrointestinal tract without biological interaction with the human body. These silicate-coating IONs are eliminated as feces.

Magnetic resonance imaging and iron oxide nanoparticles

The most important clinical application of IONs is based on MRI. The IONs exhibit both T1 and T2 effects. MR T1 effect refers to the reduction of water molecule movement frequency to the resonance state, in which the regional tissue will exhibit higher signal intensity. The MR T2 effect refers to the disruption of the magnetic field in the microenvironment, with sequential reduction of the signal intensity of adjacent tissue. The quantitative expression of the MR T1 and T2 effect is the R1 and R2 value, which is defined by the capability of reduction of the T1 or T2 relaxation time [24]. For most of the gadolinium-based contrast agents, their contrast capability is based on MR T1 effect. However, we can observe both T1 and T2 effect of the IONs that is dependent on the concentration of the IONs and the iron oxide core size. Resovist has a T1 effect in the arterial phase, in which IONs are limited in the great arteries. The MR T2 effect refers to the disruption of the magnetic field in the microenvironment. The R1 and R2 of Resovist is 72 mM^{-1} S^{-1} and 8.2 $mM^{-1}{\cdot}S^{-1}$, respectively [25]. In comparison with gadolinium-based MR contrast medium such as Omniscan that exhibiting R1 and R2 of 4.9 mM^{-1} S^{-1} and 4.8 mM^{-1} S^{-1}, the IONs has a stronger T2 relaxation effect [26]. The IONs are regarded as small magnets capable of interfering with the high magnetic field of the MRI, allowing the contrast capability to existing. Most of the IONs is taken advantage of by the T2 effect [27].

Consequently, T2-weighted sequences are preferred in the applications of IONs [28]. Recently, MR pulse sequences and magnetic particle imaging, designed specifically to IONs, have been developed [29]. The pulse sequence has higher sensitivity to the IONs and better temporal resolution with sparing the exact spatial resolution, making it the best pulse sequence for the IONs [29].

Cellular uptake of iron oxide nanoparticles

The cellular uptake mechanism varies according to the size, surface charge, and coating materials of the IONs [30]. The uptake of Resovist by macrophage (Raw264.7, THP-1) and lung cancer cell line (A549) and breast cancer cell line (MDA) is through clathrin receptor-mediated endocytosis [25,31]. The ferumoxide uptake mechanism is also through clathrin receptor-mediated endocytosis evidenced by human promonocyte (THP-1) [32]. Transmission electron microscopy of the cells ingested IONs showed iron oxide core in the

membrane-bound vesicles, and lysosomes are believed to be the organelles responsible for the metabolism of IONs [33].

Iron oxide nanoparticle on cell proliferation

In the diagnostic dose, the clinical IONs such as Resovist do not influence macrophage nor human mesenchymal cell proliferation [33,34]. Similar findings have been discovered in other clinical IONs such as Endorem® on muscle precursor cells or Feridex® on the bone marrow-derived stem–progenitor cells [35,36]. Different clinically available IONs have also been verified on the same platform, showing the inert property toward human mesenchymal stem cells (MSCs) [37]. Although there is no cellular viability change in the recommended dose, several *in vitro* studies showed enhanced cell proliferation on the Resovist-labeled cells, including human mesenchymal cells or mouse macrophage [33,34,38]. Cell proliferation is promoted through the depletion of intracellular H_2O_2, which further influences the cell cycle. These properties might have applications in tissue engineering, in which cell proliferation is anticipated.

Due to the uptake of IONs by the RES in humans, lots of attention have been paid to the RES-related cellular response after ingestion of IONs. Resovist has been evaluated toward murine macrophage (Raw264.7) cell lines or mouse peritoneal macrophages [34,39]. No cytokine release is found at the recommended dosage in these studies. However, elevated tissue necrosis factor (TNF)-α and interleukin (IL) 1-β, as well as IL-6, have been found after the cells were exposed to 100 ug Fe/mL for 24 h [34,39]. Nitric oxide secretion was also elevated under these conditions. Ferumoxides exposed to mouse peritoneal macrophage at a 100 ug Fe/mL concentration for 48 h also have a mild elevation of IL-1 after lipopolysaccharide stimulation [32]. Considering the rapid half-life of IONs in the human body and the clinically suggested dosage, cytokine release after ION injection could be neglected.

Iron oxide nanoparticles on stem cell differentiation

In addition to liver imaging, IONs have drawn plenty of attention to stem cell trafficking. The confirmation of inner properties toward cell differentiation is one of the major concerns. Studies on the Resovist toward human MSCs for bone, cartilage, and adipocyte differentiation show no differentiation capacity alteration at 100 ug Fe/mL concentration for 24 h [33]. Interestingly, under such ION conditions, human MSCs could also transdifferentiated into neuron-like cells, with electrical spiking activity being found on these ION-labeled cells [40]. The transdifferentiation of human MSCs into dopaminergic neurons after Resovist labeling is also found [41]. Feridex® along with protamine sulfate transfection shows preserved differentiation capacity on hematopoietic or MSCs [42]. These findings support using IONs as a stem cell trafficking tool under MRI.

Clinical Application of Iron Oxide Nanoparticles

Inspired by the promising *in vitro* and *in vivo* studies, several clinical trials on IONs passed the American Food and Drug Administration (FDA), European Medicines Agency (EMA), and Taiwan Food and Drug Administration. We listed IONs launched in the clinical fields and listed some IONs under clinical trials in Table 1.

Currently, IONs have been applied in medical diagnostic imaging for detecting liver tumor [27]. The most well-known IONs in the clinical fields are Resovist and Feridex I.V. In addition to liver tumor detection, IONs are also used as gastrointestinal negative contrast agents and manipulated as slow-release iron supplements for treating iron-deficiency anemia. These clinically available IONs are described as follows.

Resovist

Resovist, a T2 superparamagnetic ION, was primarily designed for liver imaging. The uptake of IONs by RES has a strong susceptibility effect that causes loss of signal intensity on T1- and T2-weighted images, making organs containing RES appear dark, primarily in the liver, spleen, and also in bone marrow and lymph nodes.

Kupffer cells in the liver take up IONs which shorten T1 and T2/T2* relaxation times. Normal liver parenchyma and lesions containing Kupffer cells include hepatic adenoma, focal nodular hyperplasia (FNH), cirrhotic regenerative nodules, and some well-differentiated nodules hepatocellular carcinomas (HCCs) usually show dark signal intensity on ION-enhanced images [45-47]. In contrast, tumors that do not contain Kupffer cells such as metastases and cholangiocarcinoma show high signal intensity on ION-enhanced images. The use of ION contrast agent in MRI is proved to be a valuable tool for differentiating between HCCs and other benign focal hepatic lesions [48-50]. A meta-analysis showed a sensitivity of 85% and a specificity of 78% [48]. Quantitative measurement of late-phase enhancement after slow Resovist administration also differentiates malignant from benign hepatic masses and hemangiomas from other focal liver lesions [51].

Differentiating HCC from FNH is among the most critical applications. Many FNH has typical image findings, such as the presence of a central scar. In some cases, they may mimic well-differentiated HCC. However, many other FNH may still show atypical findings, making the diagnosis difficult [52]. In these cases, IONs are a valuable tool in differentiating HCC from FNH [53]. This imaging strategy is of great use because a completely different treatment strategy is required for HCC and FNH.

Differentiating HCC from DN is also another important application of ION contrast for early and precise treatment of HCC in cirrhotic liver [45,46]. Histologic observations proposed that HCCs are thought to develop from a regenerative nodule to a dysplastic nodule, subsequently into a well-differentiated HCC and eventually to moderately and poorly differentiated HCC [54]. As the liver's signal intensity changes and rich Kupffer cells are positively correlated, there is an inverse correlation between Kupffer cell count and the degree of HCC differentiation, indicating that the uptake of IONs in HCCs decreased as the degree of differentiation of HCCs declined [55]. Therefore, ION-enhanced MRI may

Table 1: Iron oxide nanoparticles proved by Food and Drug Administration/European Medicines Agency/Taiwan Food and Drug Administration[43,44]

IONs proved by FDA/EMA/TFDA						
Brand name	**Generic name**	**Size (nm)**	**Surface coating**	**Indication**	**Delivery methods**	**Clinical status**
Resovist	Ferucarbotran	60	Carboxydextran	Liver tumor detection	I.V. slowly push	EMA/TFDA approval
Feridex I.V.	Ferumoxides	80-150	Dextran	Liver tumor detection	I.V. drip	FDA approval
Endorem	Ferumoxides	80-150	Dextran	Liver tumor detection	I.V. drip	EMA approval
Gastromark	Ferumoxsil	200-400	Silica	GI tract imaging	Oral	FDA approval
Faraheme	Ferumoxytol	30	Polyglucose sorbitol carboxymethylether	Iron-deficiency anemia	I.V. drip	FDA approval
NanoTherm	NanoTherm	10-15	Aminosilane	Thermal ablation of GBM	Local injection	EMA approval

IONs: Iron oxide nanoparticles, FDA: Food and Drug Administration, EMA: European Medicines Agency, TFDA: Taiwan FDA, GI: Gastrointestinal, GBM: Glioblastoma, I.V.: Intravenous

play a beneficial role in differentiating DN from poorly differentiated HCC.

Feridex I.V./Endorem

Feridex I.V. (Berlex Laboratories, USA) are FDA approved IONs coated by dextran with hydroxyl diameters of 80–150 nm. Endorem (Guerbet, Villepinte, France) is the corresponding IONs licensed by EMA. Like Resovist, the Feridex I.V. could be phagocytosed by RES in the liver, allowing good contrast between normal and tumorous liver tissue. One study focusing on the optimizing MR pulse sequence for Feridex shows that the identification of liver tumors could reach 0.3 cm [28]. However, unlike Resovist, which could be delivered by I.V. push, Feridex I.V. could only be administered by I.V. drip. For the cell labeling that is widely used in the cell therapy study, Feridex I.V. is usually mixed with a transfecting agent or protamine sulfate to enhance its labeling efficiency [42].

GastroMARK

GastroMARK is IONs coated with silica at the 200–400 nm diameter. Unlike other biocompatible IONs, GastroMARK is orally ingested and eliminated as feces. Under MR scanning, the darkening effect of GastroMARK contrasts the lumen and edematous bowel that aids in the diagnosis of inflammatory bowel disease [16]. Moreover, GastroMARK has been used as a negative contrast agent to reduce intestinal juice that could interfere with the biliary tree and pancreatic duct signals [56,57]. However, patients receiving GastroMARK experienced metallic taste that is unpleasing, which limited its acceptance in the clinical field [57].

Feraheme

Feraheme is composed of mixed magnetite/maghemite cores about 3- to 10 nm with carboxymethyl dextran coating that made up the whole particle of 30 nm [58,59]. Unlike most of the clinical application of IONs on MRI, Feraheme has been approved by the FDA for the treatment of iron-deficiency anemia. Traditional I.V. iron supplement such as iron sucrose could only be delivered in a small amount of 100–200 mg, but Feraheme could be administered at a larger amount of 510 mg [60]. The delivery amount is critical especially for chronic renal failure patient, in whom 1000 mg of iron should be given in each course. Feraheme has better dosing advantage and the incidence and severity of adverse reaction is identical to iron sucrose [60]. Owing to the clinical availability and safety evaluation, more potential applications of Feraheme have been investigated such as treating ferroportin-deficient leukemia or MR hyperthermia agent [61,62].

Translational and experimental investigations of iron oxide nanoparticles

Molecular imaging and therapy

Unlike fluorescent imaging, which can only detect tissues within centimeters, MR has unlimited tissue detection depth, making it an ideal noninvasive diagnostic tool. Moreover, the ionizing radiation-free character makes MR a better imaging modality than computed tomography for screening or follow-up. The iron oxide that is conjugated with cancer-specific targeting molecules could then be used for cancer imaging. For example, one breast cancer-specific peptide that was discovered by phage display was conjugated with IONs for breast cancer imaging. *In vitro*, *ex vivo*, and *in vivo* mouse xenografts show specific binding of these IONs to the cancer cells. Moreover, MR successfully identified these xenografts after ION delivery [63]. This conceptual diagnostic strategy has also been verified in prostate cancer and lung cancer [23,64]. The cancer-specific antibody that was used for cancer therapy, such as Herceptin, was also conjugated to IONs for specific cancer targeting [65-67]. However, these cancer-targeting effects could mostly be visualized in the *in vitro* study. The probable cause is the relatively large molecular weight of Herceptin compared with cancer-specific peptides, making it hard to penetrate the tumor capillaries. Multiple antibody binding sites to the IONs might also alleviate its potency toward cancer cells. Optimizing the targeting molecular size and the whole diameter of the IONs is still one of the challenging works.

In addition to targeted imaging, IONs exposed to alternating magnetic fields could convert these energies into thermal energy. These thermal effects could facilitate chemotherapy, radiation therapy, or immunotherapy. For example, NanoTherm, an ION with aminosilane coating, has been investigated under clinical trials for treating prostate cancer and got the FDA's approval for ablating glioblastoma multiforme [14,68].

Stem cell trafficking

There is great interest in stem cell therapy and trafficking. Once the IONs are labeled into stem cells, they could be

traced by MRI, making it an ideal strategy for validating the stem cell fate and location [69,70]. For example, in a mouse glioblastoma model, human MSCs labeled with Resovist were injected into the mouse brain and monitored for the interaction of tumor size and human MSC migration. Under MRI serial following, the glioma xenograft decreased in size, and there is significant human MSC migration toward the glioma [70]. Another example is the ischemic rat model that rat ION-labeled MSCs have injected into ventricular space. The interaction of rat MSCs with choroid plexus is found. Moreover, the ischemic stroke size of this rat MSC-treated group has greater brain recovery [69]. With the growing awareness of cell therapy in regenerative medicine, the pursuit of an ideal imaging method will trigger the development of IONs.

Immune cell trafficking

Immune cells such as lymphocytes or monocytes are circulating cells that are hard to trace. However, the accumulation of these cells is positively related to the disease process such as arthritis. Loading immune cells with IONs would be a novel strategy for monitoring disease status. By conjugating PEG-coated IONs with CD3-ab, rat arthritis could be visualized by 4.7T MRI *in vivo* [71]. Vulnerable plaque is the easily rupture plaque that contributes to acute myocardial infarction. Myeloperoxidase is an indicator for vulnerable atherosclerotic plaque. By targeting myeloperoxidase with appropriate ligand, 5-hydroxytryptamine with IONs, MRI successfully demonstrated the aortic atherosclerotic plaque in ApoE-/-mice [72]. These results might shed light on the diagnosis of inflammatory disease.

Conclusion

With the rapid progress of nanotechnology, growing numbers of IONs are entering clinical trials. The interaction between IONs and the human immune system shaped the biomedical application of IONs. Future targeted molecular imaging is anticipated based on current ION contrast agents. Slow-release iron supplements for treating anemia would be another significant advance in nanotechnology. Tumor ablation by IONs with imaging tumor capability would be other novel advances in tumor theranostics.

Financial support and sponsorship

This research was funded in part by the Taiwan Ministry of Science and Technology (MOST-110-2314-B-303-013-MY3, approved in Aug. 2021) and Taipei Tzu Chi Hospital (TCRD-TPE-109-35, approved in Jan, 2019, TCRD-TPE-106-34, approved in Jan. 2017).

Conflicts of interest

Dr. Jong-Kai Hsiao, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer-review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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