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Magnetic Nanoparticles: Its Effect on Cellular Behaviour and Potential Applications

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1. Introduction

With the advancement of nanotechnology and the development of molecular medicine, molecular and imaging becomes one of the most popular researches in the latest medicine. Molecular imaging can be defined as the imaging of targeted molecules non-invasively and repetitively in living organisms and cellular imaging can be defined similarly as the imaging of cells or cellular process non-invasively and repetitively in living organisms. At present, the common imaging tools for clinical study include ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). However, MRI is superior to CT for its better in soft tissue contrast, more sensitive in pathology detection, and lack of ionization irradiation.

In clinical practice, gadolinium-contained compound is the commonest contrast medium used in MRI study. Molecular imaging differs from traditional imaging in that contrast agents are typically used to help identify particular biomarkers or pathways with high sensitivity and selectivity (Achilefu, 2010). However, gadolinium (Gd) is not proper for the molecular imaging and cellular imaging due to its low relaxivity, that further decrease upon cellular internalization; not biocompatible and potential toxicity following cellular dechelation over time. Iron oxide (IO) nanoparticle contrast medium is another contrast medium used in clinical study. They provide the most significant signal change per unit of metal atom, especially on T2* MR imaging. Iron oxide nanoparticle are made of thousands of iron atoms in Fe_3O_4 or γ -Fe_2O_3 form so that they can increase the contrast-to-noise ratio and make its sensitivity superior to Gd contrast agent on MR examination. Their main component, oxidized iron, can be metabolized in liver and recycled as important component of red blood cells. Iron oxide nanoparticle have a relatively long circulation time and low toxicity (Bradbury and Hricak 2005; Funovics et al., 2004; Harisinghani et al., 2003; Jain et al., 2005; Montet et al., 2006). Their surfaces coating may strategically contain chemical linkage of functional groups and ligands for multimodal imaging purpose (Rogers & Basu, 2005). They can be easily detected by light and electron microscopy. Iron oxide nanoparticle posses some novel properties not seen with the other macromolecules. They can be manipulated by conjugating both targeting ligands or peptide and therapeutic components such as photosensitizer to help in diagnosis and treatment. Iron oxide nanoparticles can be used to monitor cellular migration, molecular events, and signal pathway associated with different

pathological status. Owing to its magnetic character, iron oxide nanoparticle can be manipulated magnetically and altered their magnetic character according to size of core and the condition of the coating. In this assay, we are going to review the characteristic and types of magnetic nanoparticles (MNP), especially the IO nanoparticles, the mechanism of internalization of MNP into the cell, the impact to cellular and other behaviour of macrophage and stem cell after labelling with MNP, and the future of application of MNP in nanomedicine.

2. Magnetic resonance imaging and magnetic nanoparticles

When we put a body into a strong magnetic field and then apply an external radiofrequency (RF) for a period. The RF may causes disturbance of the thermal equilibrium in the body system. After the RF stopped, MR imaging detects the different signals due to the different proton relaxation times (T) of hydrogen atom of the tissue in different body part. This makes MR offers great contrast between different soft tissues in the body. There are two types of MR imaging mechanisms: T1-weighted and T2-weighted.

T1, the ''longitudinal'' (spin-lattice) relaxation time is defined as the time required for a substance to regain the 63% of its original longitudinal magnetization after an RF pulse. It represents the correlation of frequency between molecular motions and the Larmor frequency. The frequencies of small molecule (e.g. water) and large molecule (e.g. protein) are significantly different from the Larmor frequency and thereby have long T1 and present as low signal intensity (dark) on T1-weighted images. The motion frequency of medium-sized molecule such as cholesterol close to those used for MR imaging, thereby it has a short T1 relaxation time and thus appear high signal intensity (bright) on T1-weighted images. T1 relaxation time can be shortened from the interaction between the unpaired electrons in the paramagnetic iron such as Gd ions in contrast medium and the protons in water. This makes those pathology with pooling of Gd contrast agent appear bright on T1-weighted images.

T2 is the ''transverse'' (spin-spin) relaxation time. Following a 90 degree RF pulse, the protons lose their coherence and transverse magnetization. The tissue inhomogeneity causes fluctuations of the magnetic field randomly, leading to variations in the precession frequency of different spins on x-y plane. Consequently, the net x-y magnetization is lost since the initial phase coherence is lost. This results in T2 relaxation. Thus T2 relaxation is a measure of how long the resonating protons of a substance can be changed from coherent to de-coherent and then back to coherent stage following 90 degree RF pulse in x-y plane. T2 relaxation time is defined as the time needed for the transverse magnetization decreases to 37% of its original magnitude after a 90 degree RF pulse. Generally, T2 relaxation is much less dependent on the magnetic field strength than T1 relaxation time. However, the magnetic field is not homogenous, and the process is depending on the exact location of the molecules in the magnet. In such circumstances, a special transverse relaxation time constant is defined as T2*, which is usually much smaller than T2 and highly sensitive to magnetic field strength.

The MR contrast medium can be divided into positive and negative contrast media according to their characteristic appearance on T1- weighted or T2-weighted images.

Positive contrast media appear brighter on MR images owing to a reduction in T1 relaxation time. They include those containing Gd, manganese or iron ions. Negative contrast agents appear dark on MR imaging due to shortening T1, T2, and T2* relaxation times. Iron oxide is the most common negative contrast medium used clinically.

As mentioned before, gadolinium agent is not suitable for molecular or cellular imaging. In the last 10 years, most research of molecular imaging using MRI is focused on the application of IO nanoparticle.

Compared to larger particles of the same chemical composition, nanoparticles can pass some biological barriers such as capillaries. Human albumin, a circulatory macromolecule, is similar to nanoparticles with a diameter of 5-10 nm (Wiwanitkit, 2006). Enzymes and receptors are also ranged in the similar size (Rawat, 2006). A nanoparticle of such size can have in excess of 1500 potential sites for chemical modification (Debbage et al., 2008; Harris et al., 2003) without loss of biological functionality. It is 150 times more than an antibody has. The high capacity for nanoparticle modification has led to their use as amplifiers for in vivo imaging. Both the surface properties and size of nanoparticles are important for their interaction with biological systems and therefore for their distribution in the circulation.

In considering the use in *in vivo* imaging, the ideal IO nanoparticles is with small size (5–150 nm) (table 1), high mass magnetization value, and great surface functionality. If the diameter of the MNPs is larger than 200 nm, they are usually taken up by the liver, spleen, and reticuloendothelial system and resulting in decreased blood circulation times. If their diameters are less than 5 nm, they are rapidly removed through the kidney (Gupta & Gupta, 2005). Different sizes of IO nanoparticles including SPIO (superparamagnetic IO, 60–150 nm), USPIO (ultrasmall SPIO, 10–50 nm), and MION (monocrystalline IO, 5–10 nm) can lead to different magnetic properties and function differently in various applications (Choi et al., 2006; Corot et al., 2006; de Vries et al., 2005; Thorek et al., 2006; Wang et al. 2001;).

The magnetism of MNP and its effect on MR imaging can depend significantly on their morphology, crystal structure, size and uniformity. The crystal structure of SPIO nanoparticle has the general formula of $Fe^{3+}O_3M^{2+}O$, where M^{2+}represents a divalent metal ion (i.e., iron, manganese, nickel, cobalt or magnesium) (Kateb et al., 2011). The ferric iron (Fe^{3+}) makes the complex magnetic (Daldrup-Link et al., 2003; Wang et al., 2001) and large, unpaired, thermodynamically independent spines (single domain particles) makes the complex superparamagnetic. Single domain particles or magnetic domains have a net magnetic dipole. External magnetic fields can cause the magnetic domain to re-orient. The signal intensity of these MNP is related to the size of the particle, its position, its concentration within a given voxel, data acquisition parameters, the magnetic field, and dosage of the SPIO (Wang et al., 2001). In order to achieve higher relaxivity, types of MNPs have also been designed and included those doped with alternative metals such as $CoFe_2O_4$, $NiFe_2O_4$, $MnFe_2O_4$, Gd_2O_3 and gold-coated cobalt nanoparticles (Bouchard, et al., 2009; Bridot et al., 2007; Lee et al., 2007). Magnetism in MNPs is highly sensitive to its size because it arises from the collective interaction of atomic magnetic dipoles. At a critical size, MNPs will change from a state that has multiple magnetic domains to only a single domain. Below this critical size, the thermal energy becomes comparable to what is needed for spins to flip, and the magnetic dipoles are in status of rapid randomization. Such MNPs do not have

permanent magnetic moments in the absence of an external field but can quickly respond to an external magnetic field and are referred to as superparamagnetic.

Name	Coating	Size (nm)	Relaxivity ($mM^{-1}sec^{-1}$) r_1	Relaxivity ($mM^{-1}sec^{-1}$) r_2
Feridex/Endorem, Ferumoxides AMI-25	Dextran T10	120-128	10.1	120
Resovist, Ferucarbotran SHU-555 A	Carboxydextran	60	9.7	189
Combidex/ Sinerem Ferumoxtran-10 AMI-227	Dextran T10, T1	15-30	9.9	65
Supravist SHU- 555 C	Carboxydextran	21	10.7	38
Clariscan, Feruglose NC-100150	Pegylated starch	20	n.a.	n.a.

Table 1. Examples of available SPIO and USPIO agents. Modified from Corot et al., 2006.

MION has a magnetically labeled cell probe MR imaging agent with size about 5-10nm. It has monocrystallinity and can be used for receptor-directed MR imaging. Its small size make MION can easily pass through capillary endothelium without changing its supermagnetism. It has been stated that it is possible to be detected by MR imaging at concentration as low as 1 ug Fe/g tissue. Though it is still in the experimental state, the preliminary targeted MR imaging with MION prove to be a powerful tool for cellular and molecular MR imaging in the future.

Many different chemical methods can be used for synthesizing magnetic nanoparticles. The most commonly used are precipitation-based approaches, either by co-precipitation or reverse micelle synthesis (Nitin et al., 2004; Shen et al., 1993). MNP without any surface coating are not stable in aqueous media, readily aggregate, and precipitate. For *in vivo* applications via intravenous route, these particles aggregates in blood frequently and are recognized and phagocytosed by macrophages (Lee et al., 2006). Therefore, the surface of MNP should be coated with a variety of different moieties that can eliminate or minimize their aggregation under physiological conditions. Usually, two main approaches are used for coating MNP, including in situ coatings and post-synthesis coatings (Berry et al., 2004; Horak et al., 2007; Jodin et al., 2006). With in situ coating, the MNP are coated during the synthesis process. This coating approach involves a co-precipitation process in the presence of the polysaccharide dextran and a cross linked chemically to increase its stability. This particular coating approach has been very successful in producing dextran SPIOs which are biocompatible and water – soluble. Other coatings in this class include carboxydextran coating, starch-based coating, and dendrimer-based coatings. The post-synthesis coatings can be used for coating MNP with a variety of materials, including, monolayer ligands, polymers, combinations of polymers and biomolecules such as phospholipids and carbohydrates, and silica.

Multiple MNP can also be encapsulated in liposomes to create magnetoliposomes (De Cuyper & Joniau, 1988). Polyethylene glycol (PEG)-modified, phospholipid micelles coating is favourable since this can results in satisfactory solubility and stability in aqueous

solutions, well biocompatibility, and also with prolonged blood circulation time when they are delivered intravenously. The PEG can be modified for bioconjugation of various moieties such as antibody, oligonucleotides, and peptides and may allow for molecular specific intracellular targeting of specific proteins and nucleic acid (Gupta & Gupta, 2005; Kohler et al., 2004; Kumagai et al., 2007; Lee et al., 2006, 2007a; Mikhaylova et al., 2004; Nitin et al., 2004; Veiseh et al., 2005). PEG-coated MNP has the disadvantage such as limited binding sites available for further ligand binding (Gupta & Gupta, 2005), and the coating thickness can significantly affect their relaxivity (Laconte et al., 2007). In addition to PEG coating, other materials such as antibiofouling poly(TMSMA-r-PEGMA) (Lee et al., 2006), hyaluronic acid layers (Kumar et al., 2007) and carboxylfunctionalized poly(amidoamine) dendrimers of generation 3 (Shi et al., 2007) have also been used to coat the surface of IO nanoparticles for either increasing circulation time in the blood or delivering peptides at high efficiency.

3. Impact of magnetic nanoparticles in immunologic cell

For most of the clinical imaging application on magnetic nanoparticles, the delivery route is intravenous injection. The human immune system, mostly reticuloendothelial system, recognizes these magnetic nanoparticles and ingests them. The size and surface charge of the magnetic nanoparticles determine which kind of cells that interact with magnetic nanoparticles (Moghimi & Bonnemain 1999) For particles larger than 20 nm, macrophage and Kuppfer cell is the corresponding cells that deal with MNP (Moghimi & Hunter 2001, 2005). If the MNPs are less than 20 nm, these MNPs have greater opportunity to reside in lymph nodes, after they extravasate into interstitial spaces (Moghimi & Bonnemain 1999). Currently clinical approved iron oxide nanoparticles for MR images ranged mostly from 50-100 nm, in which macrophages play important roles in ingestion of these MNPs. Macrophages are cells that prevent invading bacteria, viruses by phagocytosis of these microbes. It initiates inflammatory change by secreting cytokines such as tumor necrosis factor-alpha and interleukin 2-beta which recruits more circulating cells for repairing damaged tissue. Recent studies reveal macrophages also play important roles in tumor invasion. Consequently, alteration of macrophage behaviour has potential influence on human immunity, inflammatory process and cancer invasion. Understanding of impacts of macrophages toward ingested magnetic nanoparticles is herein clinically important.

Two different MNPs are now under clinical use. Ferucarbotran is composed of both Fe3O4 (magnetite) and g-Fe2O3 (maghemite) and coated with carboxydextran that is negatively charged. Ferumoxides is also composed of iron oxide that coated with dextran. Protamine sulfate is usually added in cell culture for more efficient ferumoxides labelling (Arbab et al., 2006).

Studies on clinically used MNPs, ferucarbotran, toward murine macrophage cell line revealed MNPs ingestion stimulates TNF-alpha and IL-2 Beta secretion. The migratory ability of MNPs laden macrophage increased but the phagocytotic activity of macrophages decreased (Hsiao et al., 2008) However, these findings are based on 100 ug Fe/mL MNP concentration that is 11 times higher than plasma concentration (Metz et al., 2004). Similar findings could be observed on murine peritoneal macrophage cultured with 100 ug Fe/mL MNPs. The secretion of TNF-alpha, IL-2 Beta and Nitric oxide, a bactericidal chemical, are

all increased in conjunction with the promotion of macrophage migration ability (Yeh et al., 2010).

Long term exposure to MNPs has significant influence on macrophages. Research on human macrophages treated with ferucarbotran show increased apoptosis after 120 hours of incubation even at the concentration of 1 ug Fe/mL. Human macrophage also shows apoptotic change when facing smaller MNPs, supravist, a smaller particle of 20.8 nm in diameter, for 120 hours at the concentration of 0.1 ug Fe/mL (Lunov et al., 2010a). The apoptotic event is inducted by N-terminal kinase (JNK) pathway that is activated by reactive oxygen species (Lunov et al., 2010a; 2010b). There is evidence that elevated TNF-alpha induce human macrophage apoptosis after these macrophages expose to ferucarbotran for 3- 5 days. However, there is no evidence that support ferucarbotran stimulate TNF-alpha secretion on human macrophage. All of studies performed above are in vitro experiments that intravenous injection of MNPs and collecting of circulating macrophage are still pending. Moreover, under intravenous injection condition, all of clinical MNPs are eliminated by reticuloendothelial system within 30 minutes in which no toxic event are observed.

Human monocyte cell line, THP-1, is a precursor of macrophage and it has been evaluated for its interaction with ferumoxides. The ferumoxides has been mixed with 1mg/mL of protamine sulfate for higher labeling efficiency. Under incubation concentration of 4.5 ug Fe/mL of ferumoxides-protamine complex for 2 hours, there is no significant TNF-alpha secretion level change upon lipopolysaccharide stimulation (Janic et al., 2008). The CD-54 and CD-83 is not upregulated in response to lipopolysaccharide.

Lymphocytes are important immune cells that regulate both cellular and humoral immunity against invading organism and cancer cells. Although lymphocytes are not easily labeled with MNPs, it is still possible by modifying surface of MNPs with tat peptide, a HIV membrane translocating peptide that is specific to CD4+ lymphocytes (Garden et al., 2006). The synthesized Tat linked MNPs are 31.3± 8.5nm which is slightly larger than original MNPs that is 25.7± 6.1 nm. Under TEM, these particles located at both cytoplasm and nucleus, which is different from other MNPs that only located at lysosomes. There is neither proliferation ability nor IL-2 secretion capability change of CD4+ CD25+ lymphocytes after labelling with tat-linked MNPs (Garden et al., 2006). Dendritic cells are antigen presenting cells that express antigens to other immune cells, mostly lymphocytes, to continue immune response. Labelling of dendritic cells allows monitoring migration of these cells in vivo (Tavaré et al., 2011; Noh et al., 2011) The mouse dendritic cells were labelled with endorem, a clinically proved MNPs in Europe with corresponding product named ferumoxide in USA. There is no drastic effect of labelled dendritic cells such as T lymphocyte proliferation, in vivo growth rate of lymph nodes after labelled or unlabeled dendritic cells labelling. Under B16 melanoma lung metastatic model, both labelled and unlabeled dendritic cells show protective effect upon pulmonary metastasis (Tavaré et al., 2011).

In conclusion, the effects of MNPs toward immune cells are diverse, the cell type, particle size, charge and labelling amount all contribute to cell behaviour change. Although some reports show immunological response change after MNPs labelling, most of the MNPs exceeds the daily clinical practice. However, systemically analysis of MNPs and immune cells interaction is important and this study may have potential impact on immune therapy.

4. Impact of magnetic nanoparticles in stem cell

Stem cells play promising roles in tissue regeneration and engineering. They could be used for tissue transplantation and it is now understand that stem cells also interact with cancer cells. Some of the stem cell promotes the growth of cancer cells whereas some animal model shows stem cell suppresses the tumor growth.

There are different types of stem cells. Embryonic stem cells are pluripotent, which means the cells could differentiate into almost all cells. However, the ethics concern and current stem cell technology progress makes it less interesting for cell labelling. Mesenchymal stem cells are multi-potent cells that could differentiate into different kinds of cells of medical interest such as bone tissue and cartilage.

Bone marrow derived mesenchymal stem cells are capable of differentiating into many tissue that is essential for tissue repair. However, when these cells delivered into damaged tissue, it is hard to differentiate where these cells are. Labelling cells with MNPs are then important to monitor the location, migration in vivo. It has been proved that MNPs labelled mesenchymal stem cells can be visualized for implantation into damaged cardiac tissue in porcine model (Kraitchman et al., 2002). In the study, ferumoxides incorporated with poly-L-lysine were incubated with swine mesenchymal stem cells and injected into myocardiocytes under X-ray guidance. Post-mortem histology shows injected cells resides in designated myocardial tissue. The labelled mesenchymal stem cells are also applied for monitoring the repair of lipopolysaccarides induced damaged brain tissue in rat model by using MNPs-tat peptide conjugate. The result shows cell migratory behaviour into the damaged brain (Jackson et al., 2010). For understanding of interaction between mesenchymal stem cells and tumor, labelled mesenchymal stem cells is also monitored for its interaction with glioma in mouse model by using ferucarbontran in conjunction with protamine sulfate and proved that mesenchymal stem cells reduce glioma growth and mesenchymal stem cells is capable of migration into glioma tissue (Chien et al., 2010).

The mechanism of MNPs uptake by different kinds of stem cells are not fully investigated but recent study shows endocytosis by clathrin receptor is one of the mechanisms (Huang et al., 2005; Lu et al., 2007). These study shows inhibitor of clathrin receptor, phenylarsine oxide, can block the ingestion of mesoporous iron oxide nanoparticles into human mesenchymal stem cells. Macropinocytosis also play significant role once if protamine sulfate is used. It is also proved that tat peptide linked MNPs enter cell by macropinocytosis (Arbab et al., 2006).

Most of stem cell labelling for MR imaging is based on T2 weighted contrast. However, some efforts aiming on T1 contrast agent such as gadolinium based chelates conjugating into mesoporous silica nanoparticles has been proved for its imaging capability in animals injected with human mesenchymal stem cells. The viability and differentiating capacity of these mesenchymal stem cells are preserved (Hsiao et al., 2008; Tsai et al., 2008). The mesoporous nanoparticles has also been labelled with fluorescent dyes that monitoring the cells with fluorescent imaging modality is also possible.

In addition to cell viability, labelled mesenchymal stem cells has been verified for its mitochondrial potential and reactive oxygen species, both of which represents intracellular stress. Neither mitochondrial potential nor reactive oxygen species change under

ferucarbotran incubation at the concentration of 100 ug Fe/mL for 24 hours (Hsiao et al., 2007). Long term incubation up to 72 hours has also been investigated and shows no adverse effect upon mesenchymal stem cells (Yang et al., 2011). Similar results are found on ferumoxide-polylysine and ferumoxides-protamine sulfate complex toward mesenchymal stem cells (Arbab et al., 2003; Pawelczyk et al., 2006).

Stem cells are valuable for its differentiation capacity. Concerns for preserving its differentiating capacity are essential. For clinical used MNPs such as ferucarbotran for directly labelling, it has been showed that labelled mesenchymal stem cells is still capable of differentiating to adipose tissue, and bone tissue at the labelling period of 24 hours (Hsiao et al., 2007). The long term effect has also been evaluated for its cartilage differentiation capacity (Yang et al., 2011). The activity of chondrogenesis of ferucarbontran labelled mesenchymal stem cells decreased as iron content increases (Hinning et al., 2009). Similar finding upon osteogenesis is also found. Dose dependent osteogenesis inhibition is observed on human mesenchymal stem cells (Chen et al., 2010). The labelling dose is consequently very important.

Labelling of mesenchymal stem cells with ferumoxides in conjunction with transfection agent is also popular. The differentiation capacity has also been studied. The adipogenesis and osteogenesis capacity is preserved but there is debate upon chondrogenesis (Kostura et al., 2004; Arbab et al., 2005). The model of ferumoxides-polylysine shows inhibition of chondrogenesis whereas ferumoxide-protamine sulfate shows no inhibitory effect. Although there is no study comparing these two labelling method, the ferumoxide-protamine sulfate and ferumoxide-polylysine complex, labelling mesenchymal stem cells with ferumoxide-protamine sulfate might be better for further investigation. Besides, labelling dose of MNPs should be suitable for preserving imaging capability and differentiating capacity.

In conclusion, labelling of stem cells for imaging is medically important that could be used for cell trafficking and potentially tumor inhibition. Although imaging capability of these labelled mesenchymal stem cells is concerned, the differentiation capacity of these cells should be preserved. Meanwhile, no satisfactory methods or consensus about labelling stem cell with MNP established though direct labelling using ferucarbotran or labelling ferumoxides with protamine sulfate are popular. Efforts on designing novel MNPs for cell labelling is still demanding.

5. Bifunctional, multi-functional, and theragnostic magnetic nanoparticles

Nanoparticles have advantages for their multi-conjugating capability that makes it possible to exhibit imaging and therapeutic character in one particle. The capability of imaging is mostly rely on the core that is magnetic. Either the shell or the core itself exhibit therapeutic effect. The therapeutic effects include gene delivery, hyperthermia, chemotherapy and photodynamic therapy. The benefits of theragnostic design are based on the following advantages. First, the magnetic core plays both imaging and magnetic guidance character. Targeting to specific organ or tissue is theoretically possible once if a guiding magnetic is applied. Secondly, the location where MNPs resides and acts as therapeutic agent can be visualized. Unlike most drugs that are small molecules, MNPs has different, specific organ and cell distribution that makes it possible for different treatment strategy. Lastly, MNPs

can traverse vasculature barrier and go into intercellular space or even cell surface once if recognizing molecules has been conjugated at the MNPs surface.

Hyperthermia with MNPs is based on the fact that tumor cells are more liable toward temperature change. It have been investigated that temperature between 41°C and 42°C can induce tumor cell death by destruction of cell membrane (Sellins & Cohen, 1991). The enzymatic system is also influenced. The hyperthermia is achieved by alternating current magnetic field system around the frequency of 100 KHz at the magnetic field intensity in 30.6 kA/m (Silva et al., 2011). Limited clinical trial was done and showed controversial effect (Maier-Hauff et al., 2007; 2011). In one study, 66 patients of glioblastoma, a high grade brain tumor, were enrolled and MNPs were injected into tumor of these patient. Hyperthermia associated with radiotherapy was done and there is statistical difference between hyperthermia group and traditional radiotherapy group. The survival after first diagnosis is 8.6 months longer in hyperthermia group compared with conventional treatment group. In addition, the adverse effect of hyperthermia is not significant according to the observation of the study (Maier-Hauff et al., 2011).

Photodynamic therapy is one of the cancer treatment methods that have also been used for theragnostic purpose. The mechanism of photodynamic therapy is based on synthesis of singlet oxygen at the expense of photon activation of photosensitizer. The produced singlet oxygen is capable of destruct adjacent cells by oxidation. Some of the photosensitizers are clinically available. Efforts trying to conjugate MNPs with photosensitizers have potential benefits such as understanding the location of drugs accumulation and MNPs can also be guided by magnetic fields. The model of multi-functional MNPs has been proved possible in vitro. Hela cells can be imaged and killed by iridium complexes conjugated iron oxide nanoparticles (Lai et al., 2008). The iridium complexes have been also conjugated to MnO based mesoporous silicate nanoparticles that exhibit T1 weighted contrast enhancement. The photodynamic therapy effect is proved efficacious at in vitro HeLa cell model (Peng et al., 2011).

Gene therapy is at the edge of new strategy for cancer therapy. MNPs is capable of serving gene delivery carrier and also used for magnetic guidance. Studies focused on cancer related gene such as E1A has been successfully delivered into HeLa cells after E1A gene incoporated with iron oxide nanoparticles. Intratumoral injection of the plasmid-MNPs complex results in tumor size reduction compared with control group, whereas only radiation therapy was done (Shen et al., 2010).

In conclusion, multifunctional MNPs are at the initial stage of development. The benefits of biodistribution and magnetic character make theragnostic strategy different from other treatment. However, more efforts upon toxicity and therapeutic range should be done before it has been used widely in the clinical medical fields.

6. Future

Cellular Imaging can be an application of MNP as cellular marker for imaging of macrophage activity and as cellular marker for imaging of cell migration and cell trafficking. With the advancement of modern molecule design, we can also have the capability of design a MNP with the role of both diagnostic and treatment.

A major limitation of IO MNP is the loss of signal on T2-weighted MRI and creating 'black holes' on images; that (1) prevent direct anatomical MR evaluation of the tissue in question (requiring comparison of pre- and post-contrast images), and (2) make it difficult to discriminate between targeted cells and image artefacts (i.e. as caused by susceptibility artifacts or imperfect pulse sequences).One such approach could be the use of a 'white marker' MR T1-weighted sequence, that creates positive MNP contrast. For cellular imaging, as labelling is not permanent and self-replicable like reporter genes, with dilution of label upon cell division, iron oxide detection may rapidly become impossible. Finally, careful iron oxide titration and cellular differentiation studies need to be performed. Short- and long-term toxicity studies are warranted. It needs a comprehensive study on the fate of the particles in vivo following biodegradation; quantify the number of iron oxide labelled molecules or cells per voxel and to increase the specificity of detection of iron oxides.

Perhaps the least studied limitation is the potential acute and chronic systemic toxicity of the particles themselves. Toxicity can result from the MNP themselves or the individual components of the MNP that can be released during degradation in vivo. Nanomaterials may influence a living organism through different biological pathways (Nel et al., 2006). From previous limited report IO MNP and gold colloids seem to be less of a concern in terms of toxicity and IO can be cleared from the body via various routes with minimal toxicity (Briley-Saebo et al., 2004; Corot et al., 2006; Jain et al., 2008). Different types of nanoparticles have been shown to be cytotoxic to human cells (Lewinski et al., 2008), induce oxidative stress (Long et al., 2006), or elicit an immune response (Dobrovolskaia et al., 2007). After administration, nanoparticles must traverse a complex and often hostile environments that have evolved to seek out and exclude foreign material (Minchin et al., 1999). The first few steps of this dangerous journey include the interacting with plasma proteins and accumulating in macrophages or the reticuloendothelial system of the liver, spleen, or lymph nodes. The types of proteins that absorb to the surface are affected by size, shape, and surface characteristics. Importantly, there is now strong evidence that the proteins that surround the nanoparticles play a critical role in determining their fate in vivo (Kreuter et al., 2002; Owens et al.; 2006, Lynch et al., 2006). Dextran is clinically approved for modifying IO MNP but liver accumulation is still evident. Silica nanoparticles have been evaluated for potential hepatoxicity because of their propensity to be taken up by the liver (Nishimori et al., 2009).Whereas large particles (>300nm) showed little adverse effects, particles less than 100 nm induced acute liver damage and cytokine release.

7. Conclusion

The nanotechnology offer great opportunities for molecular imaging and future medicine. However, they are difficulty in designing and administration. The possible acute or chronic toxicity associated with the nanoparticle is still under investigated. The implementation of nanotechnology in medicine will depend on more understand and depth knowledge about them.

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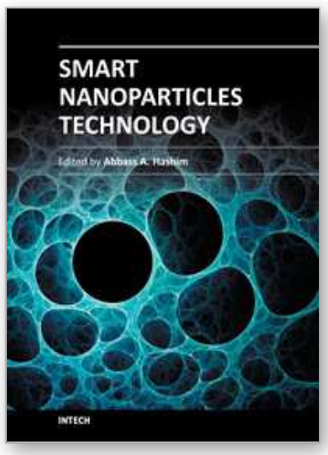

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In the last few years, Nanoparticles and their applications dramatically diverted science in the direction of brand new philosophy. The properties of many conventional materials changed when formed from nanoparticles. Nanoparticles have a greater surface area per weight than larger particles which causes them to be more reactive and effective than other molecules. In this book, we (InTech publisher, editor and authors) have invested a lot of effort to include 25 most advanced technology chapters. The book is organised into three well-heeled parts. We would like to invite all Nanotechnology scientists to read and share the knowledge and contents of this book.

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