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A Mini-Review of Magnetic Nanoparticles: Applications in Biomedicine

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ABSTRACT

Recent advances in nanotechnology have rapidly developed new therapeutic and diagnostic concepts in all aspects of medicine. Magnetic nanoparticles (MNPs) can be simultaneously functionalized and guided by a magnetic field, thus providing promising tools for several biomedical applications. MNPs contrast agents at low concentrations offer the potential to significantly improve existing methods of cancer diagnosis and treatment. In addition to imaging, MNPs can be designed so that they can selectively accumulate in cancer cells and providing "targeted" treatments that may not be possible with conventional techniques. To this end, MNPs need to have a special surface coating, which causes these materials to be non-toxic, biocompatible and targetable. The treatment of cancer by hyperthermia method could be more effective by using MNPs-based drugs, because they can manipulated under an external magnetic field and increase the efficiency of treatment due to the accumulation of these particles in tumor targets. Therefore development of MNPs could be effective for theragnostics application because they can facilitate the imaging and drug delivery and also could be useful in disease therapy. This Review provides a brief introduction to some of potential applications of magnetic nanoparticles in biomedicine especially in the detection, diagnosis and treatment of malignant tumors.

Key words: Magnetic Nanoparticles, MRI, Drug Delivery, Hyperthermia, Cancer

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Introduction

Magnetic Materials are a group of materials which are usually classified by their magnetic susceptibility (χ). The first kind of magnetic materials is called diamagnetic. Magnetic moment is antiparallel to applied magnetic field (H) and has a negative and very small χ (-10^{-6} to -10^{-3}). In paramagnetic materials, χ is in the range of 10^{-6} to 10^{-1} and magnetic moment is aligned parallel to H. Another kind of magnetic materials is ferri/ferromagnetic materials in which magnetic moments are aligned parallel to H and have a large spontaneous magnetization. M-H curve in these materials has a hysteresis loop (M is the magnetic moment per unit volume). Superparamagnetic (SP) materials are kinds of ferri/ferromagnetic materials with the size in the range of nanometer. In SP materials particles become a single domain and have higher magnetic susceptibility than paramagnetic materials. The M-H curve in these materials has sigmoidal shape without any hysteresis loop[1,2].

Due to the fact that magnetic nanoparticles (MNPs) are a group of nanoparticles that can be manipulated under the influence of an external magnetic field gradient[3], MNPs have been the subject of research over the past decade in the field of nanomedicine[4,5]. MNPs consist of magnetite (Fe_3O_4) or maghemite (γ- Fe_2O_3) and posse unique characteristics that enable researchers to use them in numerous medical applications, for instance in magnetic resonance imaging (MRI)[6,7], tissue engineering[8], drug delivery[9] and hyperthermia treatment of solid tumors[10] (Fig. 1). Among MNPs, supperparamagnetic iron oxide nanoparticles (SPIONs) had considerably been appealing in biomedicine because of their excellent biocompability and stability[11]. Since size is a main factor in engineered nanoparticles (NPs), MNPs are commonly characterized by transmission electron microscopy (TEM) for

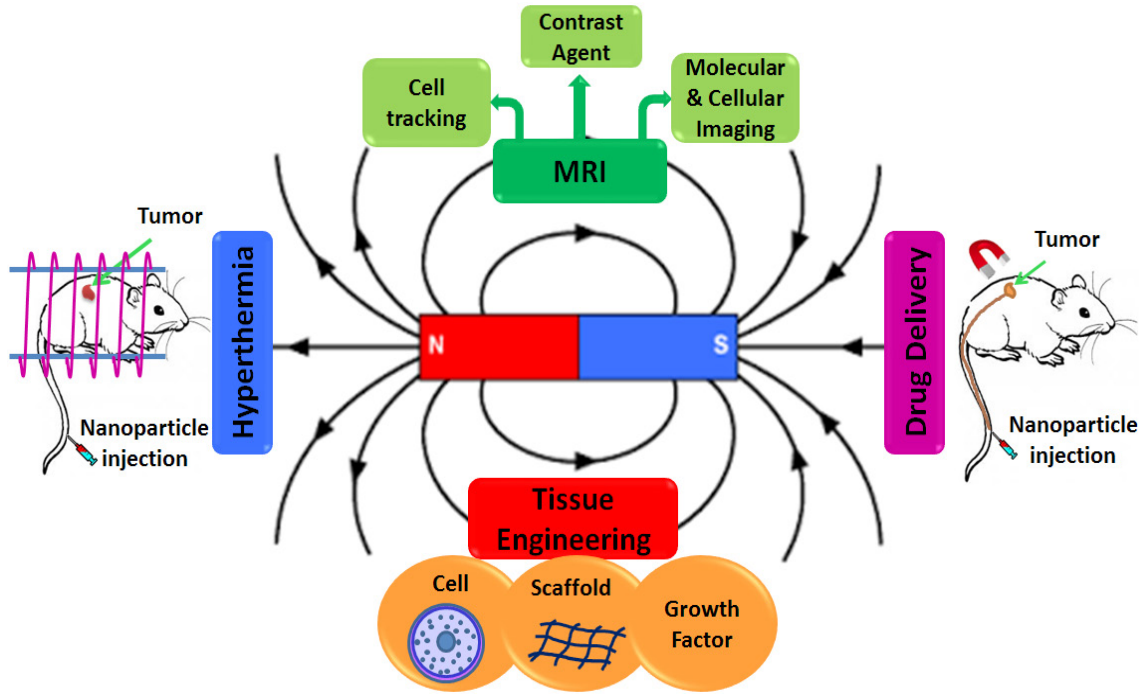

Fig. 1: Schematic representation of the different applications of magnetic nanoparticles in medicine.

determination of size and size distribution of NPs [12,13], scanning electron microscopy (SEM) for understanding the morphology of NPs, X- ray diffraction for estimation of crystalline size and crystalline structure of NPs[14], and FTIR spectra for the expression of characteristics of spectral bands to reveal nanomaterial biomolecule conjugation. The most frequently used techniques for analysis of magnetic properties are vibrating sample magnetometer (VSM) and superconducting quantum interference device (SQUID) magnetometer[15]. SPIONs have been produced by a variety of synthesis processes such as sol-gel synthesis[16], chemical coprecipitation[17], hydrothermal reactions[18], electrochemical method[19] and sonochemical decomposition reactions[20].

Each MNP is normally constructed from a magnetic core, to increase the stability of SPIONs in aqueous medium and prevent nanoparticles' (NPs) agglomeration[21]. The surface coating plays three roles: i) stabilizing the nanoparticles in a biological suspension, ii) providing functional groups at the surface, and iii) avoiding immediate uptake by the reticulo-endothelial system (RES)[22]. Several groups of coating materials such as macroclinic surfactant[23], inorganic shells[24], and polymers[25] have been evaluated for modifying the surface of MNPs.

For biomedical application of MNPs, these particles must have a small size with a narrow size distribution and must have a high magnetization value[26]. Shape, size, surface chemistry, and state of dispersion are responsible for biodistribution and toxic potential of MNPs[27]. For biomedical applications, the synthesis of SPIONs with a size less than 10 nm is highly preferred[28] because small NPs have a longer blood circulation time[29], thus providing a greater opportunity for specific localization[15].

The ability of MNPs to respond to an external magnetic field and to be functionalized has made them a useful tool for theragnostic (the combination of therapeutic and diagnostic approaches) applications[30]. In this article, a mini-review of applications of MNPs in biomedicine is presented.

Applications

Magnetic Resonance Imaging (MRI)

MRI is one of the most powerful and non-invasive imaging modalities in diagnostic medicine[31]. However, just as other imaging techniques, MRI needs a contrast agent (CA) to overcome its low sensitivity for detection of various pathological processes[32]. Recently, SPIONs have been explored for novel and negative CAs for image enhancement in MRI in T_2 weighted images. MNPs create extremely large microscopic field gradients when they are exposed to an external magnetic field. These microscopic field gradients decrease the relaxation times of nuclear spins (T_1, T_2 and T_2*) and create a dark or negative contrast in T^2 weighted images due to the susceptibility effects of the iron core[33]. For MRI imaging with MNPs, NPs should have colloidal stability and low toxicity in a biological environment[29]. To do this, NPs are coated with dextran[34], dextrin[35,36], protein[37] as CAs in MRI.

As described in the previous section, the size of SPIONs that can control the biodistribution of NPs in in vivo media is the main factor for MRI applications. Therefore, NPs with the size of above 50 nm are limited to the liver or spleen imaging because they are eliminated by the reticuloendothelial system (RES)[15]. T_2 contrast agents, such as Feridex[38] and Resovist[39] with a particle size of 120-180 nm and 60 nm, respectively, are commercially available CAs for liver imaging. SPIONs with the size of <50 nm known as ultrasmall SPIONs (USPIONs) have a prolonged half-life and are useful for detection of lymph node metastases[40] and visualization of the vascular system[41].

Molecular and cellular imaging are non-invasive imaging techniques at molecular and cellular

levels, usually related to pathology or transgene expression[42]. SPIONs are a good candidate for molecular and cellular imaging using MRI because they i) can reduce signal intensity, especially in T_2* weighted imaging, ii) are biocompatible due to their biodegradable iron core, and iii) can be magnetically manipulated[43]. In order to perform molecular imaging by MRI, ligands are required for selective binding with the purpose of creating different signal intensities from the non-targeted tissue; these appropriate ligands need to be conjugated to MRI CA. For cellular imaging, the target cells must be labeled with MRI CA in order to be clear from adjacent tissues. Imaging of enzyme activities[44] and detection of apoptosis[45] are other applications of molecular imaging with MNPs.

Specific cell tracking is another successful application of SPIONs in MRI. In vivo cell tracking aims to provide insight into the underlying biological processes existing in new cell-based therapies. Ideally, in vivo cell tracking will allow us to monitor the movement of cells between and within tissues and provides molecular information depicting cell function and viability within those tissues[46].

The use of MRI for cell tracking of SPION-labeled dendritic cells has made its way even to the clinic to monitor the dendritic cells vaccines for immunotherapy[47]. Moreover, MRI cell tracking can be used to follow the transplantation of pancreatic islet cells[48] and for monitoring new stem cell-based therapies[49].

Hyperthermia

There are numerous methods for treatment of tumors, such as administration of anticancer drugs, surgery, radiotherapy, and hyperthermia. Hyperthermia an approach in cancer therapy whereby the temper ature is increased throughout the target tissue. The viability of cancerous cells is reduced by raising the temperature of the target tissue to 42-45 °C[50] and ~ 30 min heat is enough to destroy the tumoral tissue[2], in order to damage or kill cancer cells by provoking cell apoptosis, or to make cancer cells more sensitive to the efects of radiation and/or certain anti-cancer drugs. Various methods have been employed to induce hyperthermia, including radiofrequency electric field[51], inductive heating of malignant cells[2], and use of MNPs[10].

Since MNPs can produce heat in an alternating magnetic field (AMF), they can be used for hyperthermia treatment to heat and kill the cancer cells[52]. MNPs can generate heat by hysteresis loss when placed in a high-frequency ~1 MHz magnetic field, so they allow the heating to be restricted to the tumor area[53,54]. The degree of heat generated depends on the magnetization properties of specific MNPs' formulations and magnetic field parameters[4]. For instance, selectivity of MNP uptake by tumors during hyperthermia therapy can be improved by MNPs conjugated with antibodies to cancer-specific antigens[55]. The heat achieved by MNPs due to AMF mainly depends on their specific absorption rate (SAR) values[2]. SAR is used to define the transformation of magnetic energy into heat[56] and is usually based on power losses due to Brownian and Néel relaxation mechanism[57]. Heat creation through Néel relaxation (τ_N) happens as a result of rapidly occurring changes in the direction of magnetic moments in relation to crystal lattice, while physical rotation of particles within a medium in which they are placed is referred to as Brownian relaxation (τ_B) and is hindered by the viscosity that tends to counter the movement of particles in the medium[58]. Both of these relaxation processes may occur in a ferrofluid, but τ_N is important in fixed SPM particles where no physical rotation of the particle is possible[2]. SAR values for MNPs could be predicted by using linear response models through Néel and Brownian relaxation times[59]. Reduction of the ferrofluid dose for in vivo

application is an important challenge that could be dealt with by minimizing the SAR value[60].

The SAR value is governed by Néel and Brownian relaxation mechanism and is highly sensitive to magnetic properties of MNPs (temperature dependence of magnetizations), MNPs structure (size, shape and crystal structure), and amplitude (H) and frequency of AMF[61]. A number of factors including particle size, size distribution, magnetic properties, and viscosity of fluid in which they are dispersed are important in hyperthermia with MNPs[62]. Thus, magnetic fluid hyperthermia exhibits good biocompatibility and an improvement in SAR value.

There are several studies demonstrating that hyperthermia using SPOINs could be effective for inducing complete tumor regeneration in several types of tumor model including T9 glioma in rats[63], MM46 mouse mammary carcinoma[64], and PLS10 rat prostate cancer[65].

As mentioned in this section, there are numerous factors that affect the usefulness of MNPs for hyperthermia application; therefore, numerous investigations are being carried out to optimize the characteristics of magnetic materials.

Drug Delivery

One of the most promising approaches for the treatment of cancer is magnetic drug targeting (MDT)[66]. SPIONs, e.g. magnetite (Fe_3O_4), maghemite (γ-Fe_2O_4), and other ferrites are common MNPs used for MDT because they can be guided by an external magnetic field[67]. Targeting of drugs by MNPs has been developed to reduce drug wastage, frequency of drug administration, and the potential side effects of drugs on healthy tissues[68]. Therefore, drug delivery with MNPs generally to cancerous tissues is currently investigated by researchers[69]. The first use of MNPs in delivering a cytotoxic drug was done by Widder et al. (1983) to sarcoma tumors implantedin rat tails[70].

There are two types of drug targeting into the affected tissue. The first type is passive, and the second one is active or physical targeting. In passive targeting, the distribution of the drugs is unchanged within the body and occurs through drug and carrier properties[71]. Active targeting is obtained by direct targeting of drugs and/or carriers to specific cells, tissues, or organ systems. In physical targeting, drug distribution is affected by an external factor, such as magnets in the case of SPION, or heat[72].

Drug delivery includes the following steps (Fig. 2): i) attachment of a citotoxic drug to a biocompatible MNPs; ii) intravenous injection of ferrofluid into the patient's body; iii) application of a high-gradient magnetic field for conduction of drugs to the target tissue; and iv) release of the drug in the target tissue[21]. Many parameters including field strength, depth of the target tissue, tumor volume, and rate of blood flow have significant impacts on the effectiveness of drug delivery with MNPs[73]. In general, research showed that targeting with magnetic field near the surface of the tissue and the slow blood flow are the most effective[9].

MNPs that are used for drug delivery consist of two main part: i) magnetic core to magnetic accumulation of MNPs at the target; and ii) biodegradable surface for drug reservoir to be able to release the drug[26].

Unlike traditional drugs, NPs can be designed for drug delivery because they can easily cross biological barriers[74]. Presence of the blood-brain-barrier (BBB) is a major problem in drug delivery to the brain. Since NPs can cross the BBB, nanocarriers (e.g., MNPs) could act as magnetic carriers to the brain. Since NPs can cross the BBB, nanocarriers (e.g., MNPs) could act as magnetic carriers to the brain tumors[75]. Today, MNPs have been investigated for the targeted delivery of several anti-cancer agents, and studies using MNPs for MDT still continue.

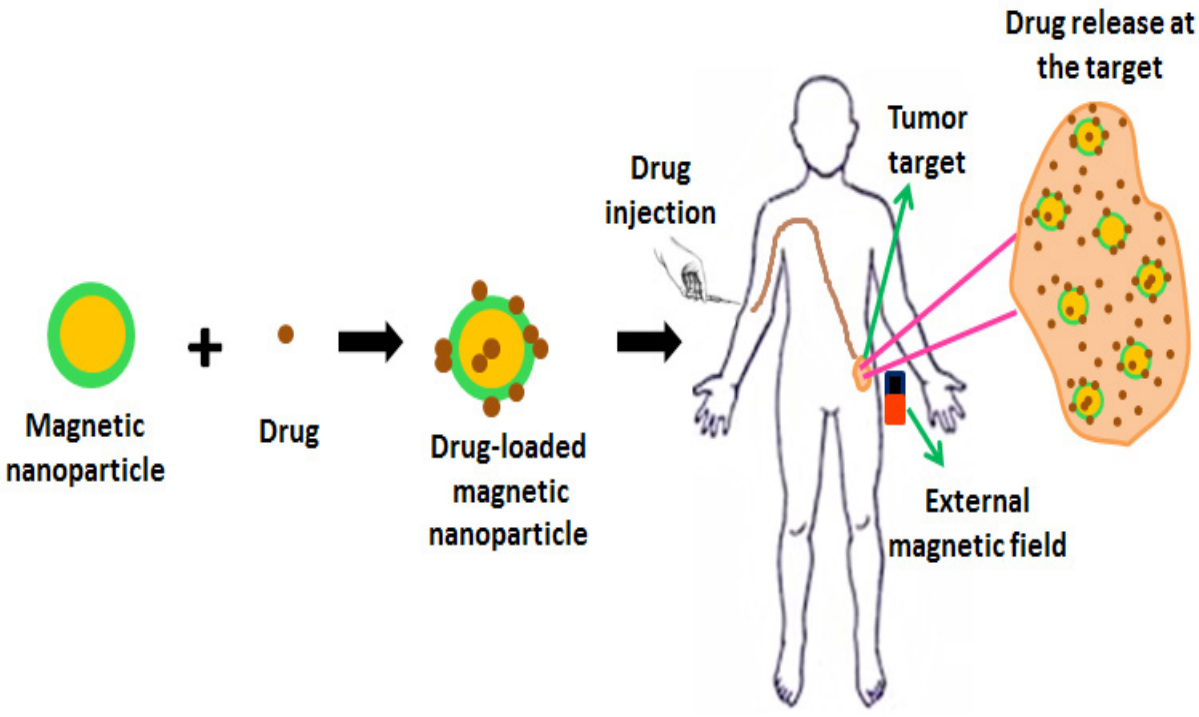

Fig. 2: Diagram of targeted drug delivery using magnetic nanoparticles.

Tissue Engineering (TE)

The limitations of conventional treatment which are essentially based on biomaterial implantation and organ transplantation could be improved by tissue engineering which benefits from principles of life science and could be conducted with MNPs. Tissue engineering is an inter-disciplinary science that offers new possibilities in functional and structural restoration or replacement of diseased or damaged tissues[76,77]. Three essential elements in tissue engineering are cell, scaffold, and growth factors. MNPs and applied magnetic fields have been employed in construction of scaffold[78]. Scaffold is a three-dimensional and biocompatible ordered microstructure used for attachment, growth, differentiation, and proliferation of cells through the use of magnetic field, and can provide controlled release of growth factor[79]. For tissue construction, the cells must be loaded with magnetic cationic liposomes or MNPs and then seeded onto scaffolds. At the end, an external magnetic field is required to be applied[26]. Monitoring grafts after in vivo implantation and determination of the fate of the embedded cells after cell labeling using SPIONs could be considered in tissue engineering applications[80,81].

Discussion and Conclusion

The application of nanotechnology has an important role in numerous areas of medicine. Here, we briefly mentioned some of the important applications of SPIONs in biomedicine, particularly in cancer detection in early stages using MRI, and treatment of cancer. Specific properties of MNPs could be used to overcome some of the limitations of traditional therapeutic and diagnostic agents. The core and coating properties of SPIONs can be manipulated for biomedical applications. To do this, various investigations are being conducted for engineering MNPs. Since the successful treatment of cancer largely depends

on its early detection, MNPs with different surface modifications can be designed for cancer imaging. For example, MNPs have been applied as an effective factor for the imaging of brain tumors. Hypointensity on T_2-weighted imaging including gradient echo imaging can appear in brain tumors after accumulation of MNPs[82]. Fu et al.[83] showed that Fluorescent MNPs can be used to improve the current state of the art in targeting and cancer molecular imaging. They can be formulated as multifunctional agents that offer imaging and molecular targeting functions, while also allowing externally enhanced localizations through the use of magnetic forces in living subjects.

MNPs are, therefore, the most suitable NPs in terms of rapid availability for in vivo human diagnostics and imaging of cancer. They also have the immense advantage of selective delivering of a drug to cancer cells[84]. MNPs are already widely used in drug delivery, transporting various agents such as antimicrobial molecules and anti-cancer drugs. For instance, Maeng et al.[85] have recently shown promising results for MNPs loaded with doxorubicin (an effective anti-cancer agent) against liver cancer in rat and rabbit cancer models.

The use of a magnetic NP platform with biotargeting agents that bind specifically to tumor cells, causes the accumulation of anticancer drugs into the cancer area. The use of MNPs' platform can increase drug concentration in the tumor and can also reveal the tumor itself in MRI. This is a very important feature, especially at an early stage of the disease, when cancer is not yet detected but there are grounds for suspecting cancer[86] Magnetic targeting can be used to drive MNPs toward the targeted cancer regions. The MNPs can also be functionalized with antibodies and proteins in order to increase their selectivity for malignant cells, therefore increasing their internalization into cancer cells[87] Results have revealed that hyperthermia treatment using MNPs can be applied for the treatment of cancer. Cancer treatment with conventional methods such as chemotherapy has certain limitations. In chemotherapy, healthy cells and normal tissues may be strongly damaged in the treatment period. Therefore, with the use of nanoparticles and especially MNPs, the dose of drug administration and its side effects can be reduced because it can be guided and released into the tumor target by applying an external magnetic field. By this method of hyperthermia treatment, we can deliver drugs to the tumor site in a high concentration, and also monitor the trend of treatment by MRI. Taking advantage of the combined thermo and chemotherapy, MNP-based therapeutic agents are certainly favorable candidates in the treatment of cancer for hyperthermia and controlled drug delivery[88]. As mentioned above, MNPs can be used for theragnostic applications. For instance, Zonghuan el al.[89] (2005) reported the first use of MNPs based hyperthermia that can also be useful for the release of encapsulated drugs.

The other applications of MNPs in biomedicine are biological labels[90], cell separation using MRI[4], and separation of biomolecules[91]. Since DNA analysis plays a key role in molecular biology, MNPs offer an opportunity for DNA separation as well[92].

Advantages of the use of MNPs in medicine include biocompatibility, selective accumulation in tumor cells, reduction of toxicity, and having a controllable size. MNPs can be designed so that they can selectively accumulate in cancer cells and provide targeted treatments that may not be possible with conventional techniques. Undoubtedly, many studies have showed that MNPs can be useful in visualizing and treatment of tumor cells by modifying their surface coating and/or functionalizing them for MDT; nevertheless, we must notice that producing a multi-tasking MNPs that can be used for theragnostic approaches is expensive. Since magnetic drug targeting can help diagnose and treat illnesses, studies to develop an MNP that can be present in significant

amounts in the target tissue and is effective for theragnostic goals are indispensable.

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