Magnetic nanoparticles: a novel platform for cancer theranostics

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Multifunctional nanoplatforms represent a cutting edge tool in biomedical applications as a result of their applicability in the concurrent monitoring of medical treatment. Magnetic nanoparticles (MNPs) have generated great interest in the field of cancer nanotheranostics owing to their intrinsic magnetic property that enables them to be used as contrast agents in magnetic resonance imaging and as a therapeutic system in conjunction with hyperthermia. In addition, the physical properties and biocompatibility of MNPs help them to act as efficient drug carriers for targeted therapeutic regimes. In this review, we have discussed the different theranostic applications of MNPs. Further, we have raised the current challenges associated with the clinical translation of MNPs along with future opportunities in this field.

Introduction

Advances in nanotechnology and molecular biology have helped to translate multifunctional nanoparticles into biomedical applications by overcoming the shortcomings related to traditional disease diagnosis and therapy. Cancer is such a difficult disease to treat because of barriers in disease diagnosis and prognosis. The unique physical properties of magnetic nanoparticles (MNPs) enable them to serve as imaging probes for locating and diagnosing cancerous lesions and, simultaneously, as drug delivery vehicles that deliver therapeutic agents preferentially to those lesions. The current efforts are being carried out to combine these two properties and to develop MNP-based nanotheranostics having imaging and therapeutic functionalities that will help toward the development of personalized medicine – with scope for real-time monitoring of biological responses to the therapy. So, there is always a need to summarize the existing knowledge and current progress on engineering of different MNPs and their applications from the theranostic point of view.

Superparamagnetic iron oxide nanoparticles (SPIONs) act as efficient contrast agents for magnetic resonance imaging (MRI) [1], as a result of high magnetization in an external magnetic field and prominent T2/T2* relaxation. In addition, there is significant scope to tailor these MNPs to have desired size, shape, crystallinity and magnetism for specific applications. Currently, a variety of MNPs are in early clinical trials and some formulations have been clinically approved for medical imaging and therapeutic applications. Some of them include: Lumiren® and Gastromark® for bowel imaging; and Feridex I.V.® and Endorem® for liver and spleen imaging, among others [2,3] (Table 1). The physicochemical properties of these MNPs provide passive targeting as a result of their nanosize, which can be increased at a higher order by addition of bioactive molecules to the MNP surface that can result in contrast agents that specifically differentiate the targeted tissue and the healthy tissues with which the drug carriers do not interact.

In the present review, we have tried to provide a brief idea about the synthesis and functionalization of MNPs, their pharmacokinetics and biodistribution properties and a brief outline regarding the strategies of targeting the MNPs to the cancer tissues. In addition, we have discussed the applications of MNPs as theranostic agents in biomedical science and some of the recent applications from a theranostic point of view. Finally, we have pointed out the current challenges for clinical translation in this field and scope for the future.

Magnetism for biomedical applications

Magnetic materials have been used in different biomedical applications for many decades. But, to use magnetic materials for

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TABLE 1

Commercially available MNPs for use as contrast agents in magnetic resonance imaging [20,28]. (Part of the table reprinted with the permission from [20]).

Number	Preclinical agent	Commercial name	MR target	Status
1	AMI25	Feridex®/ferumoxides, AMAG Pharma; Feridex I.V.®, Berlex Laboratories; Endorem®, Guerbet	Liver	Approved
2	SHU555A	Ferucarbotran, Schering AG; Resovist®, Bayer Healthcare	Liver	Approved
3	AMI227	Ferumoxtran-10/Combidex®, AMAG Pharma; Sinerem™, Guerbet	Lymph node metastases	Phase III
4	NC100150	Clariscan™, Nycomed Imaging (Part of GE Healthcare)	Tumor microvasculature	Discontinued owing to safety concern
5	AMI121	Ferumoxsil/Lumirem®, Guerbet; GastroMARK®, AMAG Pharma	Bowel	Approved
6	OMP	Abdoscan®, Nycomed Imaging	Bowel	Approved
7	Code 7228	Feraheme® (ferumoxytol), AMAG Pharma	Vasculature	Phase II

biomedical applications, they have to be superparamagnetic in nature. The superparamagnetic materials show zero residual magnetization (i.e. coercivity = zero) when removed from an external magnetic field. This helps them to avoid coagulation that, in turn, circumvents the possibility of agglomeration while being used in an *in vivo* system. Owing to the very small size, SPIONs remain in multiple discrete domains resulting in a net magnetization as a single giant magnetic moment. This renders enhanced magnetic saturation and susceptibility to the nanoparticles in an external magnetic field [4].

Under an external magnetic field, magnetic materials help the protons of the surrounding medium to relax at a faster rate thereby causing an in-homogeneity in the magnetic field. This helps these particles to be used as a contrast agent for diagnostic purposes in MRI. Another property of magnetic materials that has been exploited in biomedical science is that, in the presence of an alternating magnetic field, SPIONs show high Brownian fluctuations and show fluctuations in magnetic moment in the crystal lattice (Neel fluctuation) [5]. Brownian fluctuation and Neel fluctuations together induce heat generation known as hyperthermia, a condition that can be used as an efficient therapeutic regime.

Magnetic nanoparticles (synthesis, surface coating) and their pharmacokinetics

MNPs contain a magnetic core shell and a polymer coating that will hold the different therapeutic and targeting moieties (Fig. 1a). MNPs can be synthesized either via mechanical attrition (top down) or chemical synthesis (bottom up) processes among which chemical synthesis provides uniform size and composition to the MNPs [6]. The different chemical synthesis protocols include co-precipitation, thermal decomposition, sol–gel reaction, the polyol method, electrochemical method or sonolysis method. Although all different protocols have their own advantages and disadvantages, co-precipitation is the most popular one as a result of its ease of implementation [7,8]. Further, the surface coating plays a major part in protecting the MNPs from agglomeration, limiting the nonspecific cell interaction and also tuning the pharmacokinetics, endosomal release and drug release. In addition, surface functionalization has become an integral part of MNP designs so as to allow addition of various biomolecules. For example, amine linkers help to conjugate with acid groups of a drug, protein or DNA molecule, and carboxylic acid linkers can form amide bonds with amine groups of proteins.

To date, several polymers have been utilized to coat the MNPs that include organic polymers, for instance dextran, chitosan, polysorbate, polyethylene glycol (PEG), polyaniline and organic surfactants, such as sodium oleate and dodecylamine, and also inorganic metals, for example gold and inorganic oxides like silica and carbon [9]. Our group has synthesized MNPs using a lipid polymer glyceryl monooleate (GMO). This provides aqueous dispersion properties to the MNPs. The core size of the above formulated GMO-coated MNPs is ~10 nm [10]. Organic biodegradable dextran- and carbohydrate-derivative-coated MNPs that have been marketed for use in clinical setups include Ferridex®, Resovist®, Combidex® and AMI288/Ferumoxytol®, which are successfully used as MRI contrast agents [11].

Successful application of every nanoparticle system relies on behavior in an *in vivo* system. The pharmacokinetics of MNPs depend primarily on hydrodynamic size, charge and surface chemistry. MNPs of 10–100 nm are believed to be appropriate for intravenous (i.v.) administration; because nanoparticles >200 nm get filtered mechanically and by phagocytosis in the spleen and nanoparticles <10 nm are rapidly cleared by renal filteration [7]. In addition, opsonization and clearance of nanoparticles by the reticuloendothelial system (RES) can be avoided by providing a coating of cationic polymers or hydrophilic polymers such as PEG [12,13]. Biodistribution of MNPs is also an essential aspect to be considered, with regard to the success of targeting and for potential off-target toxicity. The toxicity of MNPs is believed to be caused by the ability of iron particles to induce the Fenton reaction, which results in production of reactive oxygen species in biological systems [14]. In addition, the toxicity of MNPs relates to the oxidation state because magnetite readily undergoes oxidation to form maghemite. However, the toxicity of MNPs can be decreased by coating MNPs, masking the oxidative sites thus making the MNPs less reactive and reducing the risk of DNA damage.

Targeting MNPs to the tumor site

Selective targeting of MNPs to the desired site is necessary to increase the efficiency of the therapeutic system as well as to avoid off-target tissue toxicity. MNPs can be selectively targeted to the