Biological Applications of IO@MS Core-Shell Nanoparticles

Subjects: Nanoscience & Nanotechnology

Contributor: Alexandre Adam , Damien Mertz

The design of core-shell nanocomposites composed of an iron oxide core and a silica shell offers promising applications in the nanomedicine field, especially for developing efficient theranostic systems which may be useful for cancer treatments.

iron oxide@mesoporous silica | core-shell nanomaterials | drug delivery | cell targeting | magnetic hyperthermia | photothermia

1. IO@MS NPs—In Vitro/In Vivo Cancer Therapy Applications

1.1. Interactions of NPs with Living Systems

Nanotechnology is quite a recent research field, and it has changed the way therapeutics are designed and formulated. Conventional injectable therapeutics exhibit some major disadvantages such as lack of selectivity, low aqueous solubility, low bioavailability, and a rapid fall in the plasma concentration due to rapid clearance of the drugs. Injectable treatments, which can deliver a sustained controlled release, would allow reducing repeated administrations and hospitalizations by maintaining therapeutic drug levels in the plasma. The size of nanoparticles and their high area-to-volume ratio, targeting ability by surface functionalization, receptor attachment, or EPR effect make these objects very suited to treat diseases such as cancers, autoimmune diseases, or diabetes. Enhanced radiotherapy, hyperthermia, targeted drugs and DNA/siRNA delivery, development of contrast agents for MRI, and CT imaging are among the new possibilities offered by injectable nanoformulations. The advantages of such injectable nanoformulations over conventional therapeutics are numerous but can also have some limitations such as difficult in-depth penetration in tumor tissues, possible early opsonization and phagocytosis, and difficult cell internalization. These latter effects will depend on the particle size, shape, surface charge, and stabilizing ligands [1].

Indeed, to bring magnetic nanoparticles further into concrete biomedical and therapeutic applications, it is necessary to have biocompatible formulations. In this frame, IO and silica are two materials of choice among inorganic materials. Arami et al. reviewed the studies dealing with in vivo toxicity of IO NPs. Many factors can influence the toxicity of the NPs, such as the mode of administration and variations between animal models or humans, but also the characteristic of the NP itself, such as the surface charge, the size, the morphology, the type of coating, and so on. However, three major characteristics of IO NPs should guarantee their clinical success:

pharmacokinetics, short- and long-term tolerability, and theranostic functionality in the desired organ [2][3]. Coated IO NPs are usually less toxic than naked particles and the coating determines the biocompatibility [3]. Silica is “generally recognized as safe” (GRAS); amorphous silica is even an FDA-approved food additive. Down to the nanoscale, some toxicity could appear due to the interaction of cells with the NPs. However, toxicology studies of silica-coated NPs have been very limited. Most of the MTT assays show that IO@MS are non-toxic due to the biologically inert surface, and silica provides a stable protective layer against oxidation and reactive species [4].

Further, R. Wang et al. recently investigated cell uptake by coupling different methods. They demonstrated that internalization is a time- and concentration-dependent phenomenon. The NPs were efficiently internalized into human osteosarcoma MG-63 cells. This complete research showed that the uptake appeared between 0.5 and 2 h and that most of the NPs were located in lysosomes [5]. This information is very important because a lot of formulations in the literature displayed a pH-dependent drug delivery. Thus, it could help to improve the design of IO@MS for DD applications.

1.2. Various Applications of IO@MS Core-Shell NPs for Cancer Therapy

In particular, core-shell NPs IO@MS, thanks to their high loading capacity, versatile surface chemistry, and intrinsic properties can find a variety of biomedical applications, and numerous publications report their in vitro and in vivo promising applications for cancer therapy [1][6][7][8]. **Table 1** summarizes different following examples.

Dual drug delivery. Recently, Sanchez-Salcedo et al. [9] investigated the simultaneous delivery of two different molecules, daunorubicin and anti-TWIST siRNA, from IO@MS core-shell NPs coated with polyethyleneimine (PEI) as anchoring layers for deposition of zwiterrionic groups. This construction showed excellent low-fouling protein adsorption and, under AMF stimulation, the co-release of the drugs resulted in improved synergistic cytotoxicity of Ovcar8 (ovarian cancer cells).

Drug delivery combined with MHT. Pon-on et al. [10] developed magnetic silica nanoparticles encapsulated in a dual pH and a temperature-responsive chitosan biopolymer NP (chitosan-g-NIPAM). Thanks to the superparamagnetic IO core, AMF stimulation can trigger the release of a DOX. A burst release is obtained at pH = 4 at 45 °C, whereas at physiological pH and temperature, the release was low. The cytotoxicity of the DOX is decreased when it is encapsulated inside the nanocomposite compared to the free DOX. Gao et al. [11] described the synthesis of IO@MS modified with a tumor-penetrating peptide and loaded with DOX. In vitro results showed the significant role of the conjugated peptide by enhancing cellular uptake and cytotoxicity of the NPs. In vivo experiments also showed a better accumulation in tumor tissue which led to an improved MRI signal and antitumor effect of DOX-loaded NPs.

Targeting ligand. The local concentration of magnetic material is crucial to have optimal localized heating when AMF is applied. Thus, the use of targeting ligands is also a very promising approach to concentrating the NPs at the disease site. Lin et al. grafted folic acid at the surface of IO@MS to enhance tumor internalization [12]. Legge et al. conjugated the surface of IO@MS NPs with antibodies to target integrin αvβ6, a well-characterized oral

squamous cell carcinoma biomarker. They showed that they were able to target αvβ6 overexpressing cells and thermal therapy through AMF application, significantly increased the killing of the targeted tumor cells compared to the control cells [13]. The efficiency of IO@MS to kill tumor cells lies also in the good internalization of the NPs, as shown already in 2010 by Saavedra et al. [14] Further, Avedian et al. [15] synthesized IO@MS NPs coated with folic acid-modified PEI and used for delivery of Erlotinib. They observed that PEI acts as a pH-sensitive coating and the presence of folic acid increased the cytotoxicity for HeLa cells.

Blood–brain barrier crossing. Glioma is the most lethal type of cancer which accounts for the majority of deaths and with very poor survival rates. Glioma treatments are mainly limited by the fact that they involve the crossing of the blood–barrier barrier (BBB), which is poorly permeable to the drugs [16]. Hegganvar et al. [17] developed an in vitro BBB model of human primary glioblastoma cells (U87 MG). They synthesized BBB-permeable nanoparticles consisting of IO@MS loaded with DOX and conjugated with a modified Pluronic F-127 bearing at its end tip transferrin (Tf) to have a sustained and targeted release of anticancer DOX. The cytotoxicity assay of this nanocomposite clearly showed a lower IC_{50} than non-loaded NPs against U87 MG cells, and thus efficient anticancer activity. Under a magnetic trigger, the nanocomposite enhanced its permeability across human brain microvascular endothelial cells, which facilitates DOX uptake.

Gene therapy. Gene therapy by DNA/siRNA delivery has a huge potential in cancer therapy, as it has unique functions, such as the knockdown of targeted genes or specific triggering of other genes. Xiong and coworkers [18] developed in this context an IO@MS core-shell NP with large pores (12 nm) in order to load siRNA and release it under AMF. The silica shell was modified by aminosilane and the global nanocomposite was coated with acid-labile tannic acid to serve as pH-responsive coating. The research showed a high loading capacity for siRNA (up to 2 wt%) and an enhanced release when a magnetic field is applied. Tannic acid provided stability and siRNA was successfully delivered into the cytoplasm of KHOS (human osteosarcoma) cancer cells in vitro in a pH-responsive manner.

Immunotherapy. Recently, immunotherapy has been expanding rapidly in the biomedical community. It is based on the strengthening or the suppression of the patient's immune system to fight disease and, in particular, to treat cancers. Zheng et al. [19] developed a nanoplatform for immunotherapy by using IO@MS coated with PEG and filled with cytosine-guanine containing oligodeoxynucleotides (CpG ODN), which can be recognized as danger signals by the immune system. However, to date, it is difficult to use free CpG ODN due to unfavorable in vivo biodistribution, a lack of specificity, and poor cellular uptake. The APTES functionalization and PEGylation allow high CpG loading capacity. They managed to activate macrophages and inhibit tumor cells when combined with chemotherapeutics while exhibiting negligible cytotoxicity in vitro. In vivo, these nanocomposites showed excellent immuno-stimulating activity.

Table 1. Table summarizing IO@MS NPs used as different multimodal platforms.

Application	Nanocomposite	Functionalization	Active Molecule	Reference
Dual drug delivery	Fe_3O_4@MS	Polyethylenimine + 2-methacryloyloxyethyl phosphorylcholine	siRNA and daunorubicin	[9]
Drug delivery combined with MHT	Fe_3O_4@MS	Chitosan-g-*N*-isopropylacrylamide	DOX	[10]
Drug delivery, dual MRI +cell targeting	Fe_3O_4@SiO_2@mSiO_2	Gd-DTPA	peptide RGERPPR and DOX	[11]
MHT + radiosensitizer +cell targeting	multicore Fe_3O_4@SiO_2	/	L-selenocystine + Folic acid	[12]
MHT + antibody-targeting	multicore Fe_3O_4@SiO_2	glutaraldehyde	Anti-αvβ6 mouse monoclonal antibody	[13]
Targeted drug delivery	Fe_3O_4@MS	polyethyleneimine	Folic acid and erlotinib	[15]
BBB crossing + drug delivery	Fe_3O_4@MS	APTES + Pluronic F-127	DOX and transferrin	[17]
Gene therapy under AMF	Fe_3O_4 nanoclusters@large pore MS	APTES + Tannic acid	siRNA	[18]
Immunotherapy	Fe_3O_4@MS	APTES+PEG	CpG ODN	[19]

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One of the main advantages to use remote external stimuli (magnetic fields, electric fields, or light) is the possibility to activate on demand the nanocomposite, in particular, to trigger the release of drugs or heating in a precise zone of the body. It also allows for sustained drug delivery and thus maintains therapeutic activity over a long time compared to the burst level of drugs by intravenous or oral administration [20]. To overcome the problem of circulating NPs as explained above, some examples of smart polymer scaffolds (hydrogels, electrospun fibers) responding to AMF and/or NIR light are detailed here, in particular for drug delivery and cancer treatment [21].

As detailed above, Fe_3O_4 magnetite NPs placed in an appropriate AMF generate heat in their surrounding environment. Satarkar et al. [22] demonstrated the possibility to use this magnetothermal effect for remote drug delivery applications. They loaded superparamagnetic IO NPs in a thermosensitive PNIPAAm-based crosslinked hydrogel with vitamin B12 and methylene blue. They were able to trigger the release of the drugs. By applying AMF for a few minutes, the temperature raised above the LCST, resulting in gel shrinkage. Campbell et al. [23] prepared a subcutaneous injectable hydrogel whose crosslinking takes place by the condensation of aldehyde-functionalized dextran with IO NPs functionalized with hydrazide-modified PNIPAAm. Gelation is rapid when both components were mixed. The gel was biocompatible in vitro and in vivo, and remote and controlled drug release was shown when AMF was applied. On the other hand, Kim et al. [24] synthesized PNIPAAm electrospun nanofibers loaded with DOX and IO NPs. After AMF application, the fibers deswelled and released DOX. It successfully induced the

death of human melanoma cancer cells (COLO 679) by the synergetic effect of hyperthermia and chemotherapy. More advanced biological studies were conducted by Xie et al. [25], who injected into mice a crosslinked chitosan-PEG hydrogel loading with DOX, docetaxel, and IO NPs. This gel showed self-healing and thermoresponsive behavior while being biocompatible. After AMF, the heating combined to the release of both drugs, which resulted in very efficient synergetic antitumor action in vitro and in vivo.

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