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Biodegradable polymer iron oxide nanocomposites: the future of biocompatible magnetism

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Superparamagnetic iron oxide nanoparticles (SPIONs) have become increasingly popular for various biomedical applications. The superparamagnetic properties of these nanoparticles enable their magnetic manipulation of biological targets such as cells, proteins and nucleic acids. In addition, SPIONs allow for MRI contrast for cells and tissues. Although generally nontoxic, these particles on their own are not sufficiently biocompatible due to their inorganic nature. One strategy to circumvent this compatibility issue is to coat the SPIONs with a biocompatible polymer. Although polymer coating is effective at mitigating potential complications at the SPION/biological interface, this only scratches the surface of the functionality that can be enabled by polymer-SPION nanocomposites. For example, polymeric nanostructures can have multifunctional drug delivery abilities, including control of the delivery of biological payloads in both space and time. An emerging strategy is to combine the advantages of inorganic SPIONs with the drug delivery capabilities of biodegradable polymeric particles to create multifunctional theranostic polymer-SPION nanocomposites. By treating the SPIONs as a cargo to be loaded into larger biodegradable

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polymeric nanostructures, new nanocomposites can be created to unite the beneficial features of paramagnetism and controlled drug release into one single nanoparticle. Biodegradable polymer iron oxide nanoparticles are promising for applications to many areas of medicine.

SPIONs in nanomedicine

SPIONs have been used primarily for three different nanomedicine applications in recent years. The first is to serve as an MRI contrast agent. Owing in part to the highly superparamagnetic nature of iron oxide nanoparticles, imaging contrast can be achieved through shortening of the T1 and T2 relaxation times in MRI [1]. The net result is a reduction in signal, which is manifested as a dark area on an MRI image. Through combination of a biological targeting agent with these particles, SPIONs can be used to detect diseased tissues or track biodistribution of various entities such as cells and drugs [1]. A second application is the use of SPIONs for magnetic manipulation of biological targets [2]. Due to the strong, inducible, hysteresis-free magnetic fields in these particles, SPIONs can lead to directed displacement of a target in a magnetic field. Such a technology can be used to collect magnetically labeled cells from a mixed population, or direct SPION bound drugs to their intended site of action [2]. The third and newest application for SPIONs in medicine is their use in targeted magnetic hyperthermia [3]. By subjecting SPIONs to an alternating magnetic field, energy absorbed by the SPIONs can be converted to heat and raise the temperature of the environment surrounding the SPIONs. The effect can be the biological destruction of diseased cells such as cancer cells [3].

Despite the promising properties of SPIONs for application in nanomedicine, these particles suffer from several critical limitations. A primary hurdle to overcome in the use of SPIONs in a biological setting is the potential toxicity associated with their administration [4]. At high concentrations *in vitro*, naked SPIONs can interfere with the cell cycle, stagnating cells in the growth phase. The decay of SPIONs into free iron also leads to concerns over iron poisoning upon repeated administration of a high concentration of SPIONs [4]. Furthermore, naked SPIONs have been shown to aggregate with serum proteins *in vivo* and be quickly eliminated from circulation by the reticuloendothelial system upon intravenous administration [1]. Limited human *in vivo* studies of dextran-coated SPIONs have led to mild side effects such as urticaria and digestive effects [4]. Taken together, these issues potentiate the need for SPION surface modifications to mitigate these effects.

Biodegradable polymer-SPION nanocomposites

A common strategy to improve the solubility and biocompatibility of SPIONs is through the use of polymers to coat the surface of the iron oxide nanoparticles, improving their surface properties for *in vivo* intravenous application. Although simple adsorption of a polymer coat such as polysaccharides, PEG and poly(vinyl alcohol) (PVA) to SPIONs has been successful to improve surface compatibility [4], a more effective and less transient strategy is to encapsulate the SPIONs in a biodegradable polymer matrix to generate a nanocomposite. Incorporation of SPIONs into a nanocomposite confers all of the superparamagnetic-related properties of SPIONs to the entire nanocomposite. In addition, these biodegradable polymer

SPION nanocomposites can be loaded with other entities as well such as drug payloads and quantum dots for functionality as therapeutics and multimodal imaging agents, respectively [5]. These encapsulated SPIONs have been shown not to interfere with particle physical properties such as size and shape, while at the same time, maintaining sufficient magnetic susceptibility to allow them to be used in varied biological applications [6].

Generally, these nanocomposites are synthesized via modified emulsion or precipitation methods that are commonplace in particle fabrication techniques. The surface character of the SPION dictates whether single emulsion or double emulsion is appropriate. For hydrophobic SPIONs, synthesized by thermal decomposition of organic iron precursors or coprecipitation followed by organic ligand capping, the iron oxide can be codissolved directly into the organic phase with any other hydrophobic drugs or molecules, and subsequently be emulsified to generate nanocomposites. Such procedures have shown to yield excellent SPION loading into poly(lactic-co-glycolic acid) (PLGA) nanoparticles [7]. In addition, SPIONs that are soluble in organic solvents can be codissolved with block copolymers for encapsulation in polymeric micelles. Hydrophilic SPIONs can also be loaded into polymeric nanocomposites; however, they require a double emulsion, water in oil in water technique to efficiently encapsulate the iron oxide. Although these composites have a lower loading efficiency, sufficient loading was noted to use these particles for magnetic contrast and this approach facilitates incorporation of hydrophilic biological molecules as well [8].

Applications of polymer-SPION nanocomposites

By uniting the controlled release and biocompatibility properties of biodegradable polymers with the superparamagnetic properties of SPIONs, numerous groups have found these composites useful for dual MRI and drug delivery functions. One example is the study presented by Li *et al.* who coencapsulated SPIONs and sorafenib into a PEG-PLGA particle that was conjugated to folic acid for targeted uptake in liver cancer cells [9]. The folate group targeted the drug-loaded nanoparticle, which led to enhanced magnetic cellular labeling and approximately fivefold reduction in cancer cell viability. Virtually no toxicity was attributed to the polymers and SPIONs, even at high saturating doses of nanoparticles [9]. Through the use of targeted nanocomposites, spatial control of imaging and therapy can be directed to a cell type of interest, such as cancer cells. SPION and curcumin-loaded PLGA nanoparticles also demonstrated efficacy against pancreatic cancer cells *in vitro*, and the effect was augmented by magnetic precipitation of the particles out of solution during incubation with cells [10]. Similarly, dual-loaded SPION and paclitaxel PLGA nanoparticles demonstrated *in vivo* anticancer efficacy in CT26 carcinoma tumor bearing mice, while simultaneously permitting these particles to be visualized by MRI [11].

Encapsulation of SPIONs within polymer matrices also permits for stimulus controlled drug delivery. Sun *et al.* synthesized a polymeric nanoparticle comprised of a poly(ethylene glycol)-b-poly(2-[diisopropylamino]ethyl aspartate) block copolymer loaded with doxorubicin and SPIONs for pH triggered drug release [12]. Upon acidification of the environment, the drug release rate was noted to be approximately ten-times higher than similar release in a neutral environment. Such a system could take advantage of the acidic

microenvironment of tumors to permit for targeted drug release [12]. In another study, doxorubicin and SPIONs were encapsulated into a polyacrylamide/polycaprolactone block copolymer nanoparticle [13]. Taking advantage of the thermal sensitivity of the polymer and magnetically induced hyperthermia, the particles were able to release drug upon induction by a magnetic field. Thus, the combined polymer-SPION nanocomposite system enabled temporal control of drug delivery via temporal control of the applied magnetic field. The magnetic field-induced hyperthermia led to a two- to threefold increase in drug release rate compared with traditional conductive heating of the particle solution [13].

Encapsulation of magnetite in biodegradable polymer matrices can also be used to study drug release and intracellular trafficking of nanoparticles. Chan *et al.* developed a method studying nanoparticle release rates from biodegradable poly- β -aminoesters [14]. By taking advantage of the differences in spin relaxation times of SPIONs when encapsulated or freely solubilized in solution, the method could resolve differences in release rates between varied particle formulations at different pH values. The authors noted that the method outperformed traditional fluorophore release procedures by increasing the sensitivity and reproducibility of the release assay [14]. Magnetic manipulation of polymeric nanocomposites has also been shown to spatially direct nanoparticles into cellular compartments of interest such as mitochondria [15]. This approach could be used to manipulate nanoparticle intracellular trafficking for enhanced spatial control and drug targeting.

Finally, SPION-loaded polymer nanocomposites have been successfully utilized in cell labeling and particle separation assays. Fadel *et al.* developed an immunostimulatory platform for cancer immunotherapy consisting of PLGA-SPION-IL-2 nanocomposites immobilized on microscale carbon nanotube scaffolding presenting immune stimulating proteins [16]. These particles were used to stimulate anticancer T cells and were subsequently separated from the T cells by magnetic decantation prior to infusion of the cells. T cells stimulated using this platform resulted in a twofold reduced tumor burden in a murine melanoma model compared with a negative control [16]. Adams *et al.* researched the utility of poly(lactic acid)-SPION composites in labeling neural stem cells for flow-based magnetic cell isolation [17]. Using high levels of encapsulated magnetite, the study demonstrated the capability of polymer-SPION nanocomposites to efficiently isolate these cells for neural regeneration without significant toxicity.

Future perspective

Given the breadth of applications reported for either SPIONs or biodegradable polymeric drug delivery alone, uniting the two results in a myriad of potential scenarios where these nanocomposites could be utilized. For example, one area of interest is gene therapy. Magnetically assisted cell transfection has already been reported in numerous applications to date and involves the use of cationic transfection reagents associated with plasmid DNA and SPIONs to achieve enhanced cell transfection. Although the possibility of polymer-coated SPIONs has been investigated by studies such as Wang *et al.*, the polymers used, such as polyethylenimine, are nonbiodegradable and potentially cytotoxic [18]. A new class of biodegradable cationic transfection polymers, poly- β -aminoesters, has been described in the past decade for highly efficient transfection of various cell types with low cytotoxicity [19].

Furthermore, these polymers have already proven to be effective at codelivery of DNA and siRNA when layered on a gold nanoparticle [20]. Development of hybrid nanocomposites containing SPIONs, biodegradable cationic polymers and anionic nucleic acids as an enabling technology to turn on and off genes in a spatially controlled and temporally controlled manner is highly attractive to combat many human diseases in new ways. In particular, a SPION-poly- β -aminoesters hybrid nanoparticle could allow for highly effective and minimally toxic nanocomposites for intracellular and theranostic gene therapy.

Another interesting consideration for the future of SPION-polymeric nanocomposites is their potential to be deformed into different shapes. While most polymeric nanoparticles and nanocomposites are fabricated into spheres due to energy minimization, techniques can be utilized to deform polymeric particles into anisotropic shapes such as ellipsoids. Recent evidence suggests that nonspherical particles permit for superior interactions with biological systems through reduced nonspecific cellular uptake and increased targeted binding and cellular internalization [21]. In addition, these nonspherical particles have been utilized in several drug delivery and immunoengineering applications and have been found to be superior to spherical particles in these capacities as well [22]. Taking advantage of these shape-based cellular interactions would be of great benefit in the future design of polymeric-SPION nanocomposites. Moreover, the ability of SPIONs to be externally activated by a magnetic field to induce heating could be utilized for inducible nanoparticle shape change as well.

SPIONs have been a popular area of research in recent years due to their capability to be applied in a wide variety of applications from magnetic contrast in MRI to magnetic cell manipulation. Given the strong understanding of these particles and their uses in biological systems, current research must be directed toward new methods to make these particles as biocompatible as possible for potential clinical translation. Encapsulation of these SPIONs in a biodegradable polymer nanocomposite not only affords superior biocompatibility, but also the functionality associated with controlled release in drug and gene delivery. Future research is needed for these materials, including critical clinical trials on how hybrid nanocomposites and their constituent components interact with and are cleared by the human body. There are also future opportunities for the use of polymer-SPION hybrid nanostructures for precision medicine where a personalized treatment, including ratiometric doses of specific drugs and/or nucleic acids as personalized genetic medicine, can be formulated with polymers into a single nanostructure along with SPIONs. Such a nanoparticle can be targeted to the site of action through specific ligands, have targeting validated by MRI, and the nanoparticle activated by a magnetic field for image-guided temporal and spatial control. Continued research into this promising technology will be beneficial toward realizing its potential in nanomedicine.

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