# Chapter 8
# A Novel Strategy for the Surface Modification of Superparamagnetic ($Fe_3O_4$) Iron Oxide Nanoparticle for Lung Cancer Imaging


**Mayank Bhushan and Yogesh Kumar**

**Abstract** Superparamagnetic iron oxide nanoparticles (SPIONs) have recently gained interest due to their low toxicity, biocompatibility, magnetic potential, and catalytic nature. Their biocompatible nature makes them suitable candidate for biomedical applications. SPIONs are considered as inert and used in different areas such as imaging, targeted drug delivery and biosensors. Their surfaces can be modified using different coating and labeling agents which has broaden their role in diagnosis and nanomedicine applications. SPIONs have got wide range of applications in biomedical and healthcare industry such as drug-delivery vehicle for chemotherapeutic drugs, an agent to induce heat mediated killing of cancer cells (hyperthermia) and as contrast agent in magnetic resonance imaging (MRI). More often SPIONs are used for simultaneous image guided delivery of chemotherapeutic drugs to the tumor cells and hyperthermia is used synergistically to enhance the overall lethal effect of the whole treatment process toward tumor cells. In this chapter, we discuss different strategies for surface modification of SPIONs and their applications for diagnosis and treatment of lung cancer.

**Keywords** SPIONs · Surface modification · Lung cancer imaging · Bioimaging

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## 1 Introduction: Superparamagnetic ($Fe_3O_4$) Iron Oxide Nanoparticle

Iron oxide nanoparticles (IONPs) are well known for their potential application in biomedicine, imaging, drug delivery, hyperthermia, magnetic separation, and cell proliferation activity. The superparamagnetic nanoparticles aggregate when magnetic field is applied but again forms stable suspension on removal of magnetic field. The most studied IONPs are magnetite ($Fe_3O_4$), hematite ($\alpha$-$Fe_2O_3$), and maghemite ($\gamma$-$Fe_2O_3$). The presence of both $Fe^{2+}$ and $Fe^{3+}$ ions in $Fe_3O_4$ NPs differentiate them from hematite and maghemite. In $Fe_3O_4$, $Fe^{2+}$ ions occupy the octahedral sites and $Fe^{3+}$ ions are divided between tetrahedral and octahedral sites. The $\alpha$-$Fe_2O_3$ contains only $Fe^{2+}$ ions which are located at octahedral sites. The $\gamma$-$Fe_2O_3$ contains only $Fe^{3+}$ ions which are distributed among octahedral sites and tetrahedral sites. The presence of electron hopping nature in these IONPs make them suitable candidate for the biological and technical applications. The surfaces of these nanoparticles can further be functionalized by coating them with suitable surface coating agents like polymers, bioactive molecules and metal oxides to increase the application specific functionality of the nanoparticles.

The major challenge in using IONPs for biomedical applications is to keep them suspended in water at pH 7.0. Several methods are used to synthesize IONPs like thermal decomposition, coprecipitation, sol–gel, microemulsion, hydrothermal, sonochemical, microwave, electrochemical, and biosynthesis. But the most common method is coprecipitation method. In traditional way SPIONs were prepared by long-term grinding of magnetite in the presence of stabilizing agent [1]. However most of the properties of these NPs depend on their shape and size. To use IONPs in vivo they must comply with features such as low toxicity, biocompatibility, long retention time and magnetism to make their application in site directed delivery. IONPs are used as a probe in magnetic resonance imaging (MRI), positron emission tomography (PET), near-infrared fluorescence (NIRF) imaging and in biosensors for detection of biomolecules like glucose, proteins, urea, and uric acid. Surface modification of superoxide nanoparticles with markers for tumor receptor such as transferrin, folate, and Her-2/neu has enabled them to specifically bind with the tumor cells. Tagging with contrasting agents can make the SPIONs suitable for the following: early detection of the disease, personalized treatment with more accuracy, effective monitoring the treatment, and the understanding of cellular interaction with the environment in the living beings. This could improve imaging in laboratory and clinic.

The presence of aligned unpaired spin of electrons in ferromagnetic materials gives rise to their magnetic properties which are not dependent on external filed. However, the magnetic properties of nonmagnetized ferromagnetic materials are dependent on the presence of external field. This happens due to presence of aligned unpaired electrons at short distance but, at long distance it is antialigned. The short distance alignment in nonferromagnetic material is also called Weiss domains. The transition between these two aligned and antialigned domain forms Bloch wall; this gives rise to single domain crystals which are thermodynamically unstable. This is

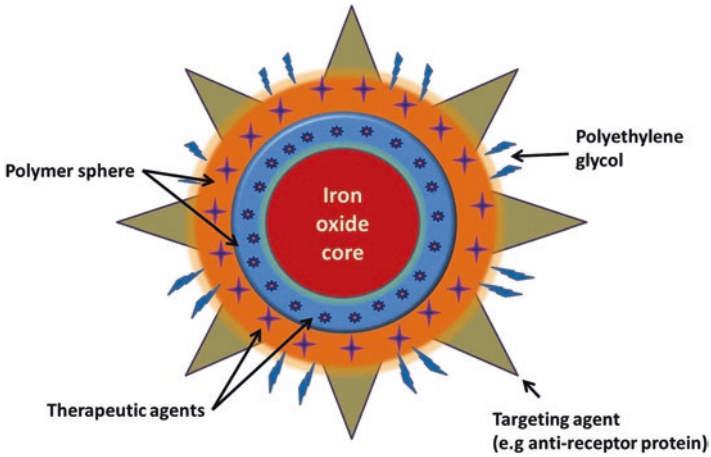


**Fig. 8.1** Schematic of drug loaded and functionalized core-shell SPION

characteristic of nanoparticles with vary small size range and their characteristic magnetic behavior is known as superparamagnetism. The magnetic resonance (MR) is not the intrinsic properties of the SPIONs. This is generated by rapid dephasing of surrounding protons in the surrounding nuclei that leads to detectable MR signal. In fact, when the SPIONs are subjected under magnetic field; their momentums align in the direction of the magnetic field. This leads to increase in magnetic flux that causes dephasing of surrounding protons. The SPIONs under magnetic field relax the longitudinal and transverse field. The ability of SPIONs to generate the MR contrast is based on reduction in spin–spin relaxation (T2) of surrounding nuclei. The SPIONs are also able to generate the T1 contrast for biomedical applications. They possess both R1 and R2 relaxivities. A schematic of drug loaded and functionalized core-shell SPION is given in Fig. 8.1.

## 2 Synthesis of SPIONs

The most popular methods for synthesizing SPIONs are coprecipitation and microemulsion. However, other approaches are also used to synthesize SPIONs with uniform diameter with desirable properties.

**Coprecipitation Method** This is the most common method to prepare magnetic nanoparticles. This involves the coprecipitation of ferrous and ferric salts in an alkaline medium. The surface complexing agent such as dextran, polyethylene glycol (PEG), or polyvinyl alcohol (PVA) is often used to provide stability and biocompatibility to the nanoparticles. Some of the surface complexing agents are listed in Table 8.1. The SPIONs are synthesized by adding concentrated base to a divalent and trivalent ferrous salt solution. The precipitate formed is isolated by magnetic

**Table 8.1** Surface coating and complexing agents

| Core nanoparticle | Surface coating | Modifier | Drug | Cell | Mechanism | References |
|---|---|---|---|---|---|---|
| SPION | | | Ursolic methyl ester | Drug-resistant human leukemia KA cells | Apoptotic staining, DNA fragmentation, | [2] |
| $Fe_3O_4$ | | | Daunorubicin | Glioma, an aggressive brain tumor | Apoptosis DNA, reactive oxygen species, DNA topoisomerase I and II, metal ions, and induction of apoptosis | [3] |
| $Fe_3O_4$ | Graphene oxide | | Doxorubicin (DOX) | HeLa cells | Hyperthermia | [4] |
| $Fe_3O_4$ | Polydopamine (PDA)-PEG | Epidermal growth factor receptor (EGFR) antibody | Doxorubicin (DOX) | | Photothermal ablation and near-infrared light-triggered DOX release | [5] |
| $Fe_3O_4$ | Poly (D,L-lactic-co-glycolic acid) (PLGA) polymers copolymer PLGA-PEG | | Doxorubicin | | | [6] |
| $Fe_3O_4$ | Diblock copolymer folate-poly(ethylene glycol)-b-poly(glycerol monomethacrylate) (FA-PEG-bPGMA), and triblock copolymer methoxy poly(ethylene glycol)-b-poly(2-(dimethylamino) ethyl methacrylate)-b-poly(glycerol monomethacrylate) (MPEG-b-PDMA-b-PGMA) | Folate was conjugated onto the surface of the nanocarriers | Cisplatin | HeLa cells | | [7] |
| $Fe_3O_4$ | PEG and PEI polymers | Folic acid | Doxorubicin | MCF-7 | | [8] |

| | | | | | | |
|---|---|---|---|---|---|---|
| $Fe_3O_4$ | Glutamic acid | Hyaluronic acid | | Targeting of CD44-overexpressing tumor cells | Receptor-meditated endocytosis | [9] |
| $Fe_3O_4$ | Amine-functionalized PEG silane | Chlorotoxin (CTX) | | | Deactivation of membrane bound matrix metalloproteinase 2 (MMP-2) and increased internalization of lipid rafts containing surface-expressed MMP-2 | [10] |
| $Fe_3O_4$ | Poly (D,L-lactic-co-glycolic acid) poly (ethylene glycol) (PLGA-PEG) | | Doxorubicin | | | [11] |
| $Fe_3O_4$ | Dextran | Folic acid | | KB cells | | [12] |

decantation or centrifugation process. To prepare bare nanoparticles by acidic method, the precipitate is treated with nitric or perchloric acid followed by centrifugation and then dispersion in water. For alkaline method, tetra methyl ammonium can be used. The obtained nanoparticles will be polydispersed, having size distribution below 10 nm and will have nearly spherical shape. The formed SPIONs can be coated with monomers and polymers through nonspecific adsorption. Many factors such as pH, heat, magnetite ratio, and polymer ratio can be used to control the size, stability, biocompatibility, and magnetic properties to make SPIONs more useful. Silica is one of the coating agents which are inert and biocompatible that can be further doped with other agent. This procedure is simple and therefore widely used at industrial level, but the nanoparticles formed are of polydispersed.

**Microemulsion Method** This method is adopted over coprecipitation method in order to adjust size and shape of the nanoparticles. In this method, the nanoparticles are synthesized in microemulsions which are oil in water and water in oil. This approach is generally used for the synthesis of biocompatible nanoparticle. This is an efficient way to synthesize nanoparticles of size range between 2 and 12 nm. The dispersion affinity of the nanoparticles in water or organic solvents can be finely tuned by adopting this synthesis approach. The coatings are suitable to make SPIONs dispersed in water can be used to prevent agglomeration.

## 3 Biocompatibility

In order to use the nanoparticles in-vivo they must be able to get cleared from the excretory system of body. Ideally, nanoparticles should have cell response with no or less cytotoxicity. Spleen and liver is most important organ to sequester the large particles. Generally particles of size 200 nm in diameter get sequestered by the spleen and liver. So, the particles like SPIONs which are of size around 10 nm easily get removed through extravasation and renal clearance. Amphipathic coatings are used to increase the half-life of SPIONs in plasma. Thus, extending their circulation time and hence effectiveness. Polymer coated SPIONs have not shown any cytotoxicity or alteration in cell adhesion behavior. PEG-coated SPIONs and dextran-coated SPIONs labeled with the Tat-internalizing peptide have not shown any effect on cell viability. Some studies have shown increase in SPIONs uptake by macrophage cells but there was no evidence of its activation because there was no interleukin-1 release.

Tumor metastasis results in leaky vasculature. It is also evident that SPIONs get accumulated at the tumor site due to the leaky vasculature and increased macrophage uptake at tumor sites. Targeted delivery of SPIONs to tumor site has been studied. The conjugation of SPIONs with specific antibodies/proteins enables them to bind directly to the cancer cells expressing that particular marker. This also facilitates the receptor-mediated internalization of SPIONs. Transferrin and Hep 2 tumor markers are most common cell surface markers expressed in cancer cells.

## 4 SPIONs in Cancer Diagnosis and Treatment

The strategy for cancer diagnosis and treatment using nanoparticles should follow the following points: high uptake by cancer cells; no or less side effect; targeted delivery; contrast between cancer and healthy cells [13].

The SPIONs are composed of an iron oxide nanoparticle core, linked with an amine-functionalized PEG silane and a small peptide, chlorotoxin (CTX) for tumor cell-specific binding of the nanoparticle. The cellular uptake of CTX bound nanoparticle was higher (98%) than the CTX unbound nanoparticle (45%). The study showed deactivation of membrane bound matrix metalloproteinase 2 (MMP-2) and increased internalization of lipid rafts containing surface-expressed MMP-2. Increased activity of MMP-2 is associated with cancer of breast, colon, skin, lung, prostate, and ovaries; the use of CTX bound nanoparticle can be for noninvasive diagnosis and treatment [10]. SPIONs and doxorubicin were encapsulated into poly (D, L-lactic-co-glycolic acid) poly (ethylene glycol) (PLGA-PEG) for local treatment. The drug loading capacity was maximum for PLGA:PEG 4000 triblock copolymer in comparison to PLGA:PEG 2000 and PLGA:PEG 3000 triblock copolymers [11]. SPIONs as MR contrasting agent were used in targeted delivery to cancer cells. KB cells (a human nasopharyngeal epidermal carcinoma cell line expressing surface receptors for folic acid) were used as positive control and A549 cells (a human lung carcinoma cell line which lacks folate receptors) were used as negative control. Dextran-coated maghemite nanoparticles prepared through precipitation method was coated with *N*-hydroxysuccinimide-folate and fluorescence isothiocyanate (FITC). The study showed that 97.5% uptake of SPION by KB cells within 1 h. And in vivo study it was delivered to the tumor site with three time efficiency than nontumor site [12].

SPIONs linked with dextran and conjugated with bisphosphonate have been synthesized for osteoporosis treatment. Osteoporosis results due to higher rate of bone resorption by osteoclast than its formation by osteoblast. The idea is to reduce the activity of osteoclast cells by incorporating nanoparticles to it and their lysis by inducing heat [14]. It has been found that, $Fe_3O_4$ nanoparticles alter the intracellular ice formation that helps to improve freezing capability. This increases the efficiency to destroy the cancer tissues. This is very helpful in cryosurgery to destroy the capillaries at the tumor edges [15].

SPIONs coated with PEG and PEI polymers and conjugated with folic acid (FA) via EDC/NHS method to target doxorubicin loaded FA-SPION at cancer site is reported. The rate of doxorubicin release was high in low pH. In vivo and in vitro treatment with DOX@FA-SPIONs to MCF-7 cancer showed tumor inhibiting effect. Aggregation of nanoparticles was monitored by magnetic resonance imaging (MRI). The nanoparticle did not show any significant toxicity on liver, lung, kidney, and heart in mice as indicated by histological examinations [8]. The SPIONs were linked with glutamic acid and conjugated with hyaluronic acid (HA). The process includes oxidation of nanoparticle surface with $H_2O_2$, followed by activation of hydroxyl group and reacting with glutamic acid as intermediate group. This is fol-

lowed by linking of HA. The study showed high survival of cancer cells and increased uptake of HA-SPIONs compared to noninteracting agarose-coated SPIONs (AgA-SPIONs) [9].

## 5 SPIONs in Lung Cancer Imaging

Lung cancer is prevalent type of cancer in developed countries like the USA. Its survival rate is less than 15%. Cancer patient survival can be increased if it is detected and diagnosed early. Currently, surgical removal of localized cancer, radiation therapy, and chemotherapy are in use. Computed tomography (CT) and positron emission tomography (PET) are also used for the lung cancer diagnosis. But, CT is associated with false positive rates and PET has low spatial resolution. SPIONs have been used to increase the spatial resolution of MRI and as T2 contrasting agent. Several formulations are already used for the liver and gastrointestinal tract imaging. An approach has been developed to combat cancer by targeting a peptide, H2009. It was successfully attached with the SPIONs with the help of PEG-cysteine moiety. The developed SPIONs have shown specificity toward α v β 6 of human H2009 lung cancer cells. But, they did not show specificity to α v β 6-negative H460 control as indicated by Prussian blue staining and T 2-weighted MR imaging. The SPIONs coated with hydrophobic surfactants resulted into stable single monodispersed particles [16]. The use of bidentate chelation and disulfide cross-linking stabilizes the surface attachment of biological molecules.

Folate conjugated poly(ethylene glycol) (FA-PEG) was linked with aminosilane-immobilized SPIONs to form FA-PEG-SPIONs. Then it was labeled with Cy5.5 to form FA-PEG-SPIONs-Cy5.5. The study carried out in KB cells and lung cancer model showed receptor-mediated endocytosis in KB cells and strong optical imaging in lung cancer model mice [17]. EGFR-targeted, inhalable SPION nanoparticles were developed for non-small cell lung tumor ablation. The principle lies in the hyperthermia to generate heat by magnetic SPIONs. The result showed retention of SPION nanoparticles in the tumor which significantly inhibited in vivo lung tumor growth [18]. Cis-diamminedichloroplatinum (II) is a chemotherapeutic agent that has some side effects specially affecting kidney and its distribution is nonspecific. A magnetic CDDP-encapsulated nanocapsule (CDDP-PAA-NC) with CDDP-polyacrylic acid (PAA) core in amphiphilic polyvinyl alcohol/superparamagnetic iron oxide nanoparticles shell was developed which significantly reduce toxicity and exhibit anticancer activity in A549-tumor bearing mice with negligible side effects [19]. Endothelial progenitor cells (EPCs) can be utilized for cancer ablation and to repair vascular injury. EPCs were labeled with *N*-alkyl-polyethylenimine 2 kDa (PEI2k)-stabilized superparamagnetic iron oxide (SPIO) to facilitate magnetic resonance imaging (MRI) of EPCs in a mouse lung carcinoma xenograft model. It was injected intravenously and subcutaneously (mixed with A549 cells). The extension of labeled EPCs was found inside tumor cells, as identified by MRI. This showed excellent biocompatibility and MRI sensitivity [20]. A folate

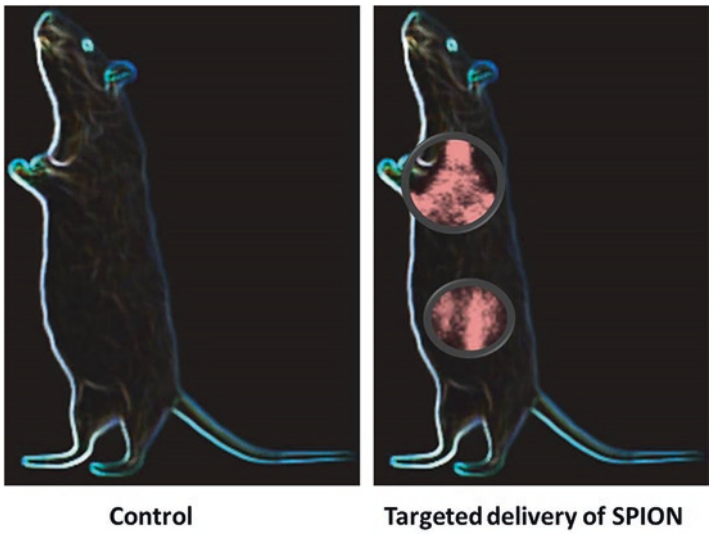


**Fig. 8.2** Schematic of targeted delivery of SPIONs at lung cancer site and their subsequent accumulation in liver and kidney in mice

receptor-targeting multifunctional dual drug-loaded nanoparticle (MDNP) has been developed that contains a poly(*N*-isopropylacrylamide)-carboxymethyl chitosan shell and poly(lactic-co-glycolic) acid (PLGA) core for enhancing localized chemo-radiotherapy to effectively treat lung cancers. This showed controlled release of encapsulated therapeutic compounds (NU7441—a potent radiosensitizer, and gemcitabine). The study showed the use of nanovesicle in dual-mode simultaneous chemotherapy and radiation sensitization for lung cancer treatment [21]. EGFR targeted anticancer gene, plasmid-survivin/shRNA (pshRNA) albumin SPION complex were designed for the monoclonal antibody-dependent gene targeting in lung cancer therapy [22]. A schematic of targeted delivery of SPIONs in mice cancerous lung and their subsequent accumulation in liver and kidney is given in Fig. 8.2.

## 6 Conclusions

Magnetic resonance imaging plays a vital role in diagnosis of internal disease and injury. Because of their good contrast agent characteristics, SPIONs have become a means for MR imaging of tissues, cells and even of intracellular structures/molecules. The bioconjugation chemistry has pushed the boundaries of usability of SPIONs beyond molecular imaging for detection and quantification of genes, cell tracking, molecular and enzymatic interactions, etc. Effective imaging approaches such as MR, optical imaging using semiconductor quantum dots and nuclear are in

large demand because of the ongoing discovery of new class of genes and proteins in oncology. This requires study of ever-increasing genes, protein molecules and associated molecular pathways in order to provide diagnosis and treatment of cancer. However, the lack of techniques for effective, accurate, and noninvasive imaging of molecular interactions in biological systems prevents us to exploit the biological knowledge at full potential for the treatment of disease. With persistent advancement in SPIONs as molecular imaging probes in the areas like cost reduction, non-complex conjugation chemistry, enhanced target affinity, and as a means for MRS to minimize sequestration in lysosomes, the magnetite nanoparticles continue to display their significant potential as a means to probe further into biological systems.

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