Chapter 6
Superparamagnetic Iron Oxide Nanoparticles (SPIONs) as Multifunctional Cancer Theranostics

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Abstract Nanobiotechnology stemmed from the recruitment of tools developed by nanotechnology to be applied in many other sectors, including nanomedicine. Particularly, magnetic nanoparticles (MNPs) are of great interest, having successfully offered controlled sizes, capability to be manipulated externally, localized magnetic hyperthermia treatment (MHT), and enhanced magnetic resonance imaging (MRI). As a result, these MNPs are used as therapeutic and diagnostic tools in a variety of biomedical applications such as cancer, Alzheimer, and bacterial infections. In this regard, novel insights provide rationale for designing and development of superparamagnetic iron oxide nanoparticles (SPIONs) to be utilized in various biomedical applications, especially given that SPIONs are already used in clinical trials in late phases. These magic nanoparticles opened avenues to drug delivery, cellular-specific targeting, multi-modal imaging, and a new era of personalized medicine for management of cancer. Herein, we will unravel the extra-unique properties of SPIONs endowing the multifunctional characteristics and abilities for diagnosis, therapy, and online therapeutic monitoring that are referred to theranostics. Moreover, huge efforts have been exerted recently on designing and developing of SPIONs with enhanced biocompatibility, safety, drug-loading capacity, stability, and imaging ability. In addition, the minimization of cellular uptake by macrophages, preferential targeting of cancerous cells sparing normal cells, monitoring cancer cells prior to and after treatment, as well as triggering therapeutic drug release in a controlled fashion envisioned SPION as a golden therapeutic era tool. Overall, this book chapter will highlight the state-of-the-art designed SPIONs, their fabrication, characterization, and the mechanism of their action in targeting cancer cells.

Keywords SPIONs · Cancer · Theranostics · Drug delivery · Diagnosis · Magnetic · Nanoparticles

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Introduction

Cancer is described as the worst monster nightmare for all humanity. It is characterized by uncontrolled cell proliferation, evasion all tumor suppressors, invasion, metastasize, immortality, angiogenesis, and evasion of host defense mechanisms of immune system (Hanahan and Weinberg 2000; Hanahan and Weinberg 2011). Meanwhile, cancer deaths increases exponentially, and according to the WHO, the expected deaths number by 2030 is 13.1 million (Stewart and World Cancer Report 2014). Herein, the real prerogative is to use multifunctional nanotheranostics for effective diagnosis, imaging, and treatment of cancer. This challenge is achieved by using superparamagnetic iron oxide nanoparticles (SPIONs) (Yigit et al. 2012; Rosen et al. 2012; Tong et al. 2011). SPIONs are considered as the most promising tool in cancer theranostics as they are characterized by a superparamagnetic behavior, stability at physiological pH, non-toxicity, biocompatibility, and biodegradability. Also, they are metabolized easily and transported by trans-ferritin, ferritin, and hemosiderin to endogenous iron reservoir to be used later for hemoglobin synthesis. Besides, SPIONs are very small in size (1–20 nm) and having large surface to volume ratio. Moreover, they are characterized by reactive surface that can be easily modified with biocompatible capping agents. Their surface could also be potentiated via covalently attaching to ligands, antibodies or peptides for targeted drug delivery (Zou et al. 2010). What is really exciting here is the multifunctional ability of SPIONs for improving cancer therapy. There is a great potential lies within the in vivo imaging by (MRI), hyperthermia, magnetic separation, biosensing application, tissue repair, and targeted drug delivery (Dilnawaz et al. 2010; Veiseh et al. 2010; Perez et al. 2002; Frullano and Meade 2007; Corot et al. 2006; Solanki et al. 2008).

SPIONs Design for Cancer Theranostics

Precise design of SPIONs can lead to the formation of a smart multifunctional nanocarrier specific for personalized medicine via combining the therapeutic, diagnostic, and targeted drug delivery ability in a single biodegradable and biocompatible particle. Basically, SPIONs are formed of three main layers (Fig. 6.1): the first layer (core), which is formed of iron oxide and acts as MRI contrast agent, the second layer (capping layer), which is usually biocompatible and biodegradable material preventing aggregation, and the third layer which is the therapeutic coating with targeted moiety.

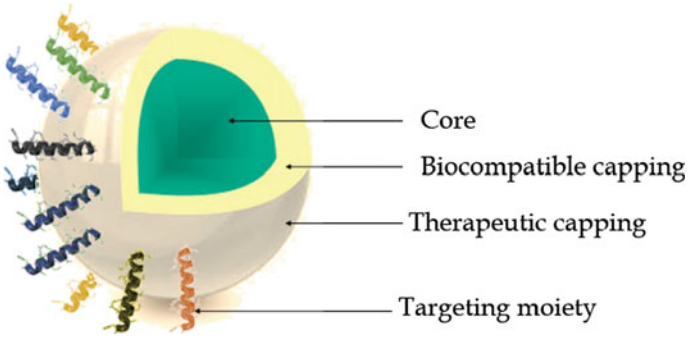

Fig. 6.1 Schematic illustration of SPIONs design for cancer theranostics

SPIONs Structure and Types

SPIONs are considered as a pivotal therapeutic and diagnostic tool in cancer treatment in addition to their ability to overcome the multi-drug resistance and many of the drawbacks of conventional chemotherapy approach of cancer treatment, such as biocompatibility, poor solubility, and hydrophobicity of the anticancer drugs. Basically, SPIONs consist of core made from iron oxide and a coating material. Herein, there are three types of SPIONs core—maghemite (γ-Fe_2O_3), hematite (α-Fe_2O_3), and magnetite (Fe_3O_4)—with the magnetite being the prevailing one among others. Substantially, magnetite contains Fe^{2+} and Fe^{3+} ions with molar ratio 1:2. Ostensibly, magnetite is of great importance as it triggers Fenton reaction that leads to the formation of reactive oxygen species (ROS) in cancer cells (Huang et al. 2013) (Fig. 6.2).

Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + OOH^{\cdot} + H^{+}$$

Strikingly, SPIONs exhibit superparamagnetic characteristics below 30 nm size at room temperature. In this regard, superparamagnetism can be defined as the ability of magnetic nanoparticles to show paramagnetic nature with intensive saturation and susceptibility magnetization under the effect of magnetic field and the tendency of losing this nature totally once the magnetic field is removed leading to zero coercivity and zero magnetic remanence.

Concomitantly, SPIONs surface at the very small size is so reactive due to the increased surface area-to-volume ratio. As a result, SPIONs surface is dominantly coated with capping agent or surfactant or even polymers to prevent their aggregation in colloidal solutions and to preserve fixed shape and size. Otherwise, SPIONs will aggregate and settle down forming bulk structures in colloidal solutions. However,

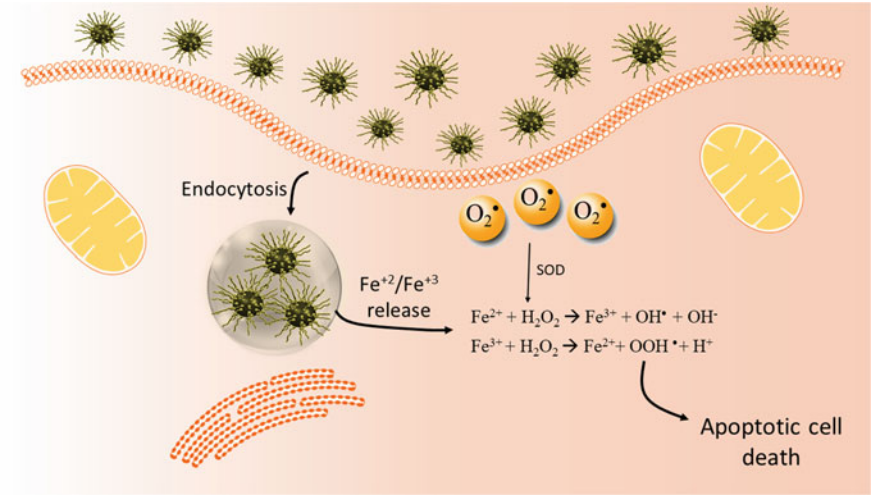

Fig. 6.2 Schematic illustration of SPIONs initiated fenton reaction and ROS formation

these coating materials affect the superparamagnetic properties of SPIONs depending on their amount, nature, composition, and thickness.

SPIONs Synthesis Methods

SPIONs have been fabricated using different techniques including physical, chemical, and microbial methods. The chemical methods are mainly utilized and they are favored over other fabrication approaches. In this section, we report the commonly used wet chemical methods for SPIONs fabrications, preceded by a summary for each method's advantages and disadvantages as illustrated in Table 6.1.

Co-precipitation Method

Co-precipitation method is a facile and convenient approach for the fabrication of SPIONs from aqueous solutions of Fe^{+2}/Fe^{+3} salts (in a 2:1 stoichiometric ratio) by the addition of a base under inert atmosphere at room or an elevated temperature (70–90 °C). It has been quite established that in order to obtain monodispersed particles, a burst nucleation followed by a slow controlled growth should be achieved. The size, geometry, and composition of SPIONs are highly depending on the type of salt used (chlorides, sulfates, nitrates), reaction temperature, ferric and ferrous stoichiometric ration, ionic strength, and pH of the solution. Vikram et al. demonstrated that the Fe^{2+}/Fe^{3+} ratio and the rate of base addition also affect the magnetic properties of the resulting SPIONs (Vikram et al. 2015) that may lead to particles with

Table 6.1 Common synthesis methods of SPIONs

Method	Synthesis conditions	Reaction temperature (°C)	Reaction period	Solvent	Size distribution	Shape	Yield
Co-precipitation	Very simple and ambient condition	Room temperature up to 90	Minutes	Aqueous	Quite narrow	Not so good	High
Thermal decomposition	Hard, inert atmosphere	100–320	Hours-days	Organic	Very narrow	Good	High
Hydrothermal	Hard, ambient condition	220	Hours-days	Aqueous-ethanol	Very narrow	Very good	Medium
Microemulsion	Simple, ambient condition	20–50	Hours	Organic/aqueous	Relatively narrow	Good	Low
Sonochemical	Simple and ambient condition	Room temperature	Minutes	Aqueous	Quite narrow	Not good	Medium
Microwave	Simple and ambient condition	Microwave irradiation	Very fast	Aqueous	Quite narrow	Not so good	Medium

ferromagnetic properties instead of superparamagnetism. In order to obtain small and monodispersed particles, organic additives such as surfactants or capping agents are used during the synthesis (Bee et al. 1995; Ishikawa et al. 1993). For instance, SPIONs with narrow sizes of 4–10 nm can be stabilized in aqueous media of 1 wt% polyvinyl alcohol (PVA) (Lee et al. 1996). The main disadvantage of this synthesis method is the formation of polydispersed and improper crystalline SPIONs which highly affects the saturation magnetization value to be in the rage of 30–50 emu/g and lower than the bulk magnetization value of 90 emu/g. Nevertheless, SPIONs with monodispersed size of 9 nm were obtained via co-precipitation method using a tetramethylammonium hydroxide (Cheng et al. 2005).

Thermal Decomposition

Inspired by a well-established approach of thermal decomposition for the synthesis of well-defined semiconductor nanocrystals and oxides in organic media (Murray et al. 1993; O'Brien et al. 2001), modified methods for the synthesis of highly crystalline and monodispersed SPIONs with a control over sizes and shapes have been developed. The method involves the thermal decomposition of an organometallic precursor in the presence of a surfactant (such as oleic acid) and organic solvent with elevated boiling points (Maity et al. 2009). The resulting SPIONs tend to disperse only in non-aqueous solvent by the hydrophobic–hydrophobic interaction between the surfactant and the solvent. The concentration of the precursor and surfactant, reaction temperature, stoichiometric ratio of precursor to surfactants, and the reaction time are highly affecting the magnetic and physicochemical properties of SPIONs. Given that different applications, especially biomedical applications, require SPIONs to be rendered water soluble, this can be achieved by ligand exchange method (Lam 2016; Korpany et al. 2016; Xu et al. 2011) or bilayer surfactant stabilization method (Xu et al. 2011; Maity et al. 2008).

Hydrothermal Method

In hydrothermal approach, SPIONs of uniformed sizes and shapes can be synthesized by dissolving the precursors in an aqueous media alongside with surfactants under maintained high pressure and temperature in a pressure autoclave vessel. Adjusting heating temperatures, reaction timing and precursor to surfactants ratio influence the sizes, shapes, and magnetic characteristics of the resulting SPIONs. Mitchell et al. successfully prepared ultrafine SPIONs using hydrothermal route to be used for high-performance energy materials. Their electrochemical analysis also encouraged their potential application as ultra-capacitors (Mitchell et al. 2014). However, this fabrication route often yields in moderately crystalline particles in a prolonged time frame compared to other synthesis methods such as thermal decomposition method.

Microemulsion Method

Another reported method for SPIONs synthesis is the microemulsion approach where two immiscible micro-domains are thermodynamically stabilized by an interface layer of surfactant. The microemulsion systems used for synthesis of different nanoparticles are either water-in-oil (w/o) or oil-in-water (o/w) system. In w/o microemulsions (frequently used for synthesis of SPIONs), the aqueous phase microdroplets of iron oxide reactants are stabilized and protected by a monolayer of surfactant migrated from the continuous oil phase. Wang et al. have synthesized magnetite nanoparticles using a modified single microemulsion method. The magnetite nanoparticles have an average size of 10 nm and showed perfect supermagnetism with high Curie temperature, T_c value of 860 K (Liu et al. 2004). Nonetheless, this method produces a wide range of magnetic nanoparticles without full control over the sizes and shapes. Furthermore, the working window is quite limited when compared with other previously reported methods. Also, this synthesis approach requires large amount of solvents, which narrows its large-scale practice.

Sonochemical Method

SPIONs can be synthesized by sonolysis of organometallic precursors in the presence of organic additives (surfactants/capping agents) to control the growth of particles (Durdureanu-Angheluta et al. 2010). Sound energy creates cavitation of microbubbles in aqueous media where unusual reactions occur leading to the desired products (Ashokkumar et al. 2007). The physicochemical characteristics of the produced nanoparticles can be controlled by varying the irradiation power and time. Dolores et al. demonstrated a linear increase in the production of SPIONs with refluxing time at a constant sonication frequency (Dolores et al. 2015). Sodibo et al. studied the required amount of time (from 1 to 20 min) for sonochemical capping of SPIONs with 3-amino propyl triethoxylsilane (APTES). The results showed that the surface functionalization was achieved only after one minute of refluxing under ultrasonic irradiation (Sodipo and Aziz 2018). Nevertheless, thermolysis methods usually yield in crystalline nanoparticles while sonolysis usually produce amorphous nanoparticles (Pinkas et al. 2008).

Microwave-Assisted Synthesis

Microwave-assisted synthesis gained a great attention in recent years as a green synthesis technique (Kijima et al. 2011). In a fractional time and low energy consumption, microwave irradiation results in successful fabrication of SPIONs from iron salts. Bano et al. reported the microwave-assisted synthesis of stable SPIONs functionalized with PEG-6000 with a size range of 17–25 nm (Bano et al. 2016). The

main drawback of this fabrication tool is the shorter crystallinity time and homogeneous nucleation period which can be attributed to the uniformed heat distribution of microwave that leads to reduced surface reactivity (Pascu et al. 2012).

SPIONs Capping

It is noteworthy that naked SPIONs are highly unstable in water and at physiological pH, and tend to aggregate and rapidly precipitate. Furthermore, uncapped SPIONs could be easily engulfed by phagocytes as foreign bodies. Thus, significant attentions have been paid to SPIONs capping, as it acts as a protected shield from the immune system giving it stability, increase the circulation time, and enable their conjugation with targeting moieties. Substantial summary of the most common capping agents for SPIONs is described in Table 6.2.

Table 6.2 Most common SPIONs capping agents

Capping agent	Characteristics	Application	References
Chitosan	Hydrophilic, biodegradable, and biocompatible	Contrast agent for MRI	(Hong 2010)
Silica	Transparent, biocompatible, and reduced toxicity	Contrast agent for MRI	(Alwi et al. 2012; Ren et al. 2008)
Polyacrylic acid	Increases cellular uptake	Cell labeling for MRI	(Vetter et al. 2011)
Dextran	Increases cellular uptake, enhances stability, and biodegradable	In vivo cell tracking, contrast agent for MRI	(Yu et al. 2012; Tassa et al. 2011)
Polyethylene glycol (PEG)	Increases stability, reduces nanoparticles aggregation, biocompatible, biodegradable, and water soluble.	MRI, gene and drug delivery, and bio-labeling	(Yu et al. 2012; Allard-Vannier 2012)
Polyethyleneimine	Offers high positive charge and high cellular uptake	MRI, gene and drug delivery, and sensing	(Cen 2019; Hoang MD 2015; Kim et al. 2017)
Polyvinyl alcohol	Biocompatible, biodegradable, hydrophilic, and increases stability	MRI, gene and drug delivery	(Nadeem M 2016; Bannerman et al. 2017)

SPIONs and Therapeutic Payload

The ultimate goal of cancer therapy is to eradicate cancer cells leaving normal cells healthy and unaffected. Thus, the chemotherapy is developed everyday as a marathon runner. However, most of the known chemotherapy can elaborate unsolicited side effects to healthy cells. At this glance, targeted drug delivery and integration between SPIONs and chemotherapy could limit the side effects to normal cells. Furthermore, it could prolong the circulation time, achieve maximum targeting efficacy and sustain the release of the therapeutic molecules.

Successful integration between therapeutic payload and SPIONs includes several design strategies:

a. Conjugation of the therapeutic payload to SPIONs surface.
b. Physical interaction through co-encapsulation of therapeutic payload into coating material of SPIONs.

The first approach is conjugation, where cleavable bond between therapeutic molecule and SPIONs is created like amide (CO-NH_2), hydrazone (CN-NH), and disulfide bond (S-S) (Nigam and Bahadur 2017; Shang et al. 2017). The advantages of this approach include enhancing the loading efficiency and protection of therapeutic drugs to maximize its effect. Furthermore, it is suitable for conjugation of peptides and proteins to protect them from oxidative degradation. Basically, several chemotherapies have been conjugated with SPIONs like doxorubicin, paclitaxel, and methotrexate (MTX) (Shaghaghi et al. 2019; Kang et al. 2018; Moura et al. 2014).

The second approach is the physical interaction through co-encapsulation of therapeutic payload into coating material of SPIONs. It occurs via electrostatic interactions or hydrophilic–hydrophobic interactions. As an example, the SPIONs coated with positively charged polyethyleneimine (PEI) interact electrostatically with negatively charged DNA (Tutuianu R 2017). In addition, SPIONs coated with hydrophobic polymers can strongly interact with hydrophilic drugs where the drug molecules are released when the coating material degrade. The main advantage of this approach is the ability to overcome the low entrapment efficiency and limited stability.

Role of SPIONs in Cancer Theranostics

SPIONs act as theranostics particles that can perform multiple functions at the same time such as diagnosis, targeting, and treatment. The pivotal role of SPIONs is not only improving diagnosis but also increasing the efficacy of cancer treatment as illustrated below:

SPIONs in Diagnosis by MRI

Unraveling the complexity of magnetic resonance imaging (MRI) is of great importance. Substantially, it is a spectroscopic technique based on the principles of nuclear magnetic resonance (NMR) and used for imaging of deeper tissue in human body. Thus, it is considered as a vital non-invasive tool for cancer diagnosis (imaging and tracking) (Turkbey et al. 2010; Morrow et al. 2011). However, the obtained MRI images of abnormal and normal tissues are very difficult to differentiate between them. Therefore, exogenous contrast agents are in urgent need to increase sensitivity, image contrast, and acquiring higher resolution (Fig. 6.3). For this purpose, SPIONs are designed and used as contrast agents that should have the following criteria to be used as MRI imaging probes (Qin et al. 2007; Wei et al. 2017).

a. Magnetism: SPIONs should exhibit higher magnetization when exposed to external source of magnetic field. Furthermore, the magnetization should return to zero when the external magnetic field is removed.
b. Well-designed surface coating: This includes the integration of targeting moieties to SPIONs surface such as peptides, proteins, antibodies, targeting ligands, carbohydrates, polymers, aptamers, RNA, and DNA. These targeting moieties will enhance the specific targeting to the tumors.
c. SPIONs water solubility is very important factor to avoid any aggregation.

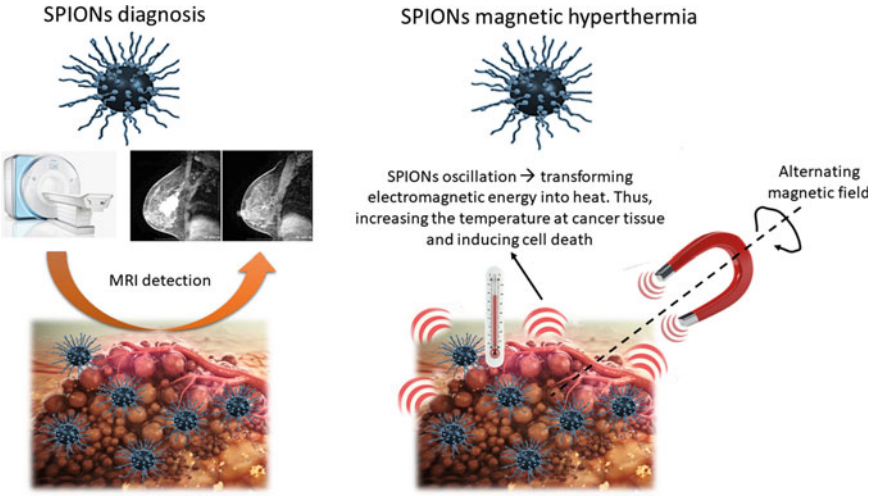

Fig. 6.3 Schematic illustration of SPIONs role in cancer theranostics: diagnosis and magnetic hyperthermia

SPIONs in Cancer Treatment

Efficient cancer therapy remains the hardest challenge facing scientific community. Thus, hyperthermia emerged on scene as an effective method for cancer treatment. In this regard, when body tissue is exposed to elevated temperature ranging from 42 to 48 °C, the tumor cells are more sensitive and susceptible to damage than normal cells. Thus, tumor cells will undergo apoptotic death. Preponderance of literature indicated that apoptosis can take place when temperature range of 42–46 °C is applied, while necrosis can happen when temperature exceeds the 46–48 °C range. Such therapeutic strategy is limited only to tumor cells thus minimizing the harm to normal cells (Ding et al. 2017).

It is noteworthy to mention that SPIONs act as heat generators. In this context, the magnetic targeting is used to localize SPIONs at the tumor site. After that upon exposure to alternating magnetic field for certain time, SPIONs generate heat of about 42–45 °C inducing apoptotic cell death that is called magnetic hyperthermia (Fig. 6.3). However, heat generation varies and depends on the shape, size, SPIONs crystallinity, magnetic properties, and the applied magnetic field. Herein, the efficiency of SPIONs magnetic hyperthermia is measured by specific absorption rate (SAR) that converts the magnetic field into heat (Chen et al. 2011).

SPIONs Coinciding with Other Therapeutic Agents

Grouped with Photodynamic Therapeutic Agents

A widely used method for cancer tackling is photodynamic therapy (PDT) where a light source and a photosensitizer agent are utilized to initiate photonecrotic effect for tumor cells by selectively producing reactive oxygen species in those tissues. Generally, SPIONs are used as supporting cargos to deliver photosensitizing agents for combined imaging with MRI, magnetic navigation, and PDT. Recently, Ostrokonkove et al. (Ostroverkhov et al. 2019) successfully loaded different bacteriochlorin-based photosensitizers on human serum albumin (HSA) coated iron oxide magnetic nanoparticles (IONPs). In vitro and in vivo studies demonstrated the stability of the fabricated nanoparticles and their capabilities to deliver photosensitizer to malignancies guided by MRI. Similarly, Yan et al. (Yan L 2018) directly immobilized a photosensitizer protoporphyrin IX (PpIX) for PDT within SPIONs for diagnosis by MRI without the use of any additional carriers, thereby high loading capacity of the therapeutic agent was achieved. Their practice at the in vivo level showed a significant reduction of the tumor growth rate. Du et al. (Du et al. 2018) co-delivered a natural photosensitizer phycocyanin alongside with a synthetic photosensitizer hematoporphyrin monomethyl ether (HMME) on the surface of IONPs. The in vivo and in vitro results demonstrated a significant inhibition of MCF-7 breast cancer cells proliferation upon exposure of near infrared (NIR) irradiation. In another

study, pheophorbide (a photosensitizer agent) conjugated acetylated hyaluronic acid (PAH) was used as a surface coating for magnetic NPs to target integrin CD44 over-expressed in breast cancer cells. The self-assembled NPs showed higher biocompatibility and water solubility. In vitro studies showed that PAH@MNPs enhanced heat generation (up to 43 °C) and singlet oxygen production when exposed to external magnetic and laser irradiation (Kim et al. 2016). In addition, SPIONs was combined with carbon fullerene (C60) and HMME as a nanocomposite system. In vitro studies showed a 23-fold enhancement in its therapeutic efficacy (Shi et al. 2013).

Grouped with Photothermal Therapeutic Agents

Photothermal therapy (PTT) recently gained greater interests as a non-invasive, selective, and controlled therapeutic approach in tumor treatment. Compared with photodynamic therapy, PTT do not generate reactive oxygen to cause damage to cancer cells. Rather, PTT cause thermal ablation of cancer cells by converting the light irradiation (in the wavelength of infrared and longer ranges) into heat. The therapeutic efficacy of the photothermal agents (PTAs) highly depends on their ability to transform light into sufficient heat enough for the thermal ablation of cancer cells. Therefore, SPIONs were extensively reported in combination with other PTAs such as gold and graphene oxide. Recently, Salaheldin et al. (Salaheldin et al. 2019) examined the photothermal efficacy of graphene/IONPs (G/Fe_3O_4) nanocomposite when exposed to 808 nm infrared laser excitation. Interestingly, a significant reduction of HepG2 cell viability was observed at the in vitro level. Ghaznavi et al. (Ghaznavi et al. 2018) reported the fabrication of core-shell Au@IONPs coated with PEG. When tested at the in vitro level, a significant lethality was observed for KB nasopharyngeal cancer cells (around 62%) and MCF-7 breast cancer cells (around 33%) following exposure to 808 nm laser irradiation. Wang et al (Wang Y 2018) fabricated a multistage photothermal-based nanosystem by coating IONPs with polydopamine as a PTT agent. Eyvazzadeh et al (Eyvazzadeh et al. 2017) studied the effect of using core-shell Au@IONPs for enhanced PTT. The MTT essay on KB cell showed substantial cell lethality (up to 70% cell death) following the photothermal treatment. Fu et al. (Fu et al. 2014) used Prussian blue dye (as a PTT agent) coated SPIONs for the photothermal treatment of HeLa cells. The blue-colored dye showed significant mortality by killing up to 80% of tumor cells and substantial tumor inhibition rate around 87.2% upon exposure to NIR irradiation.

Grouped with Sonodynamic Therapeutic Agents

Sonodynamic therapy (SDT) found its comprehensive biomedical applications. Cancer treatment performed using mechanical waves of ultrasound in the presence of sonosensitizer. SDT agents such as TiO_2 and HMME get activated upon exposure to ultrasound waves to produce reactive oxygen species triggering the cancer cells death.

Compared to PDT, using SDT for cancer treatment is preferred due to the higher tissue penetration of ultrasound irradiation, especially in solid tumor tissues, than the NIR irradiation. An increasing interest is developed in using magnetic nanoparticles in combination with sonosensitizers to enhance the cancer treatment efficacy. Zhang et al. (Zhang et al. 2018) compared the ability of a sonosensitizer chlorin e6 (E6) alone and in combination with PEG-IONPs (PIONPs) as a coating for the production of intracellular ROS sufficient enough for cancer cells ablation. They found out that IONPs@E6 substantially increased the generation of ROS compared to the use of free E6. Moreover, the E6 coating onto the surface of PIONPs significantly enhanced its solubility and bioavailability. Shen et al. (Shen et al. 2015) reported the use of multifunctional nanosystem of Fe_3O_4@TiO_2 and DOX for a combined therapy of SDT by TiO_2 NPs and chemotherapy by DOX in presence of Fe_2O_3 as a guiding tool by MRI. This combination showed a superior anticancer effect when compared by their solo utilization. Interestingly, Niu et al. (Niu et al. 2013) prepared SPIONs@PLGA microbubbles in combination with DOX for dual delivery of therapeutic agents (SDT and chemotherapy) and dual imagining by ultrasound/MR for the treatment of metastatic lymph nodes at in vivo level.

Other Usages of SPIONs in Biomedical Applications

SPIONs for Alzheimer's Disease Diagnosis and Therapy

Alzheimer's disease is considered as the most devastating neurodegenerative disorder that prevalent among people over 65 years of age. It is generally marked by the amyloid plaques. Attributed to the unique characteristics of SPIONs such as high ability to pass through biological barriers, high surface, and ease of surface decoration with ligands of choice, they are progressively utilized as potential candidates for Alzheimer's disease diagnosis and treatment (Krol et al. 2013). Cheng et al. (Cheng et al. 2015) reported the use of SPIONs surface modified with curcumin (SPIONs-Cur) as a detection tool of amyloid plaques. A further coating with PEG was applied so as to enhance particles' circulation. Interestingly, SPIONs-Cur were capable of localizing the amyloid plaques. Bellova et al. (Bellova et al. 2010) found out magnetite nanoparticles significantly reduced the amyloid aggregations of lysozyme in vitro which makes them good as therapeutic agents for the prevention of amyloid fibrillogenesis. Luckily, the encouraging research highlights of the nanoparticle usage in this field paved the way for new diagnostic/therapeutic agents to overcome the reported limitation of the current approaches in clinical practice.

SPIONs Against Bacterial Diseases

Antimicrobial resistance against antibiotics is widely considered as a serious global health issue (Kruijshaar et al. 2008; Snell 2003). Frightening figures are described of estimating that by 2050 about 300 million death incidence will be caused by antimicrobial resistance strains as well as heavy economical loss approximated to be around $ 100 trillion (Munita and Arias 2016). In this regard, different nanotherapeutics entailing antimicrobial activities have been studied. Magnetic nanoparticles physicochemical properties such as their relatively simple synthesis methods, innate antimicrobial activity, and most importantly their biocompatibility favored their usage as antimicrobial agents (Torres-Sangiao et al. 2016; Malekkhaiat Haffner and Malmsten 2017). Moreover, the magnetic nanoparticles' surface could be functionalized to actively target the microbes (Jallouk et al. 2015; Zazo et al. 2016; Mohammed et al. 2016). For example, SPIONs functionalized with cationic moieties succeeded in capturing over 97% of bacteria (Huang et al. 2010). Although the antimicrobial activities of nanomaterials are not fully understood, they are mostly working according to the following mechanisms: damage the cell membrane due to mechanical stress caused by the particles themselves, intriguer loss of microbial protein functions by releasing toxic metals, and incite reactive oxygen generation damaging the microbial DNA, RNS, and protein (Reddy et al. 2012; Huang et al. 2014).

Conclusion

The reported advantages of SPIONs paved the way for their greater practice in the medical and clinical fields. A wide range of different formulations was developed for imaging, diagnosis, and treatments of different biomedical diseases. SPIONs characteristics and so their functions are mostly determined by their fabrication method. Therefore, selecting the synthesis method is one of the most important aspects of their usage so as to control the SPIONs size and shape. Furthermore, the surface coating highly affects SPIONs' biocompatibility, stability, and targeting capabilities, providing a mean to control their physical characteristics and surface chemical activity. In addition, surface modification help escape the phagocytes, which substantially increase their circulation time, and works as an anchor for further surface decoration with targeting ligands and peptides to enhance their affinity to target sites and cells. Overall, the success of using SPIONs in drug delivery and MRI applications increased the interest of their utilization in advanced theranostic clinical applications. Nevertheless, further studies are needed to improve their targeting, reduce their toxicity, and enhance their stability in vivo.

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