CHAPTER 10

Tumor-Targeted Therapy

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10.1 INTRODUCTION

The World Health Organization (WHO), according to the world cancer report, has predicted that by the year 2020, due to the increase in cancer incidence, there is an estimation of around 60% more deaths and every year there will be about 15 million new cases of cancer incidence [1]. Investigators are collaborating globally in developing specific approaches through multidisciplinary efforts to cure primary and secondary tumors and particularly thwart the spread of metastatic events with multimillions of dollars' investments including pharmaceutical companies. Most cancer-related deaths occur due to metastasis when vital organs are affected by the malignant cells. In fact, the hallmarks of cancer are frequently perceived as any inflammations that are unresolved due to the irregular biological events that distinguish as an initiation of cancer cells within the tumor microenvironment (TME) [2]. It is predominantly caused by any alteration in specific genes that changes the normal cellular functions.

Cancer, which is also known as malignancy, tends to exhibit an abnormal uncontrolled growth of cells with the potential to invade neighboring cells and spread throughout the body. Not all tumors are cancerous, and an exception includes the benign tumors that don't spread to other regions of the body. The classifications of cancers are typically based on the cell type that is similar to tumor cells and imply the tumor origin. Advancements in technologies have led to the identification of hundreds of cancer types including nonmelanoma skin cancer, melanoma, breast cancer, lung cancer, colorectal cancer, prostate cancer, bladder cancer, kidney cancer, sarcomas, and non-Hodgkin lymphoma [3–13]. Leukemia is a slow-growing cancer type showing rapid progress in its symptoms. Leukemia is also known as blood cancers that show excessive production of specific white blood cells that mix with bloodstream and are sometimes chronic as well. After

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numerous DNA mutations, the normal cells tend to proliferate uncontrollably with unregulated growth spreading far through distant invasion, causing metastasis through the blood vessels or lymphatic drainage systems. Therefore, early diagnosis and precise targeting and evaluation of cancer are the biggest challenges of today.

10.2 NANOTECHNOLOGY AND CANCER THERAPY

Scientific progress in nanotechnology has led to the advancement of a variety of contrast-enhancing nanoparticles based on multimodality imaging and applications [10,11]. Over the decades, many magnetic nanoparticles have been developed for studying cancer tracking, detection, staging, and targeting [14,15]. These are primarily used to study molecular and cellular targeting, to probe the angiogenic progression, and to track the pathways of immune cells such as T cells, macrophages, and monocytes. Investigators are deeply probing the biological system transformation to understand how the molecular and cellular mechanisms alter from the healthy state to a cancerous state. The discovery of cancer biomarkers has fueled the study of rapid uncontrolled tumor growth and the in-depth investigation of the mechanisms that initiate the origination, the maintenance, and the progression of cancer. Biomarkers are commonly termed as a distinguishing feature that is usually independently measured and assessed as an indicator of normal biological, pathogenic, or pharmacological responses in response to a target or therapeutic intervention. Over the decades, the discovery of biomarkers has changed the paradigm of standard of care and empirical treatment strategies to personalized cancer therapy. These biomarkers are based on numerous factors such as pathogenic tumor-specific genotypes and genetic profiles as well as pathogenic mechanisms [16]. Pathogenesis of a disease is referred to as the biological mechanism that leads to the abnormal state. The pathogenesis illustrates the origin and development of disease that may be acute, chronic, or recurrent. Pathogenicity is the ability to characterize a genetic constituent of a pathogen and the ability of an organism to damage the host to make the situation vulnerable to cause disease.

Target therapies are aimed to track the tumor-specific cell targets both through endogenous agents or exogenous agents and over a period of time. This is very challenging due to the lack of underlying mechanisms and the greater complexity associated with their tumor-microenvironment interplay and host interactions, their delivery route, migration, dose escalation, stability, and safety. On the other hand, the drug-delivery systems (DDSs) are

designed in accordance with the nanoparticle structures' core platforms such as macroparticle, nanoparticle, and ultrasmall nanoparticle. Bioconjugation of nanoparticles is allowable when the composition and combination of components are put together in appropriate relationships or structures by specific formulations. The bioconjugation permits the binding of target-specific biomolecules and drugs for diagnostic and therapeutic as well as nanomedicine applications. The DDSs also have the abilities to enhance the interaction of biocompatibility and absorption through bioavailability and pharmacokinetics during therapeutics [17]. For differentiating tumor from normal cells and tissue, therapeutic deliveries of these nanoparticles through encapsulation with drug were performed via injection to organs. Nano-drug-delivery systems (NDDs) were also considered to release many nanocarriers [18]. This is well suited to accelerate the drug solubility and efficacy, easy passage within blood-brain barrier (BBB), and biochemical stability. Since the pathophysiological distinctiveness of most tumors differs based on their complexity, such as increased angiogenic hot spots with aggressive vasculature and associated heterogeneity, the chaotic vascular architecture, abnormal lymphatic drainage, and extensive creation of permeability mediators, the NDDs are preferred. Furthermore, as reported by Maeda and coworkers, the enhanced vascular permeability and retention effect provide greater efficiency by NDDs on a time-dependent manner for controlled release of drug and regulate the deprived conditions such as the nutrients and oxygen to the rapidly growing tumor.

Nanoparticles are often defined by their sizes, which are often smaller than 100 nm. Generally, the composition of nanoparticle is characterized by solid colloidal particles that may consist of an assortment of materials of biochemical nature, such as biomolecules, liposomes, dendrimers, carbon, metals, metal oxides, silicates, polymers, or inorganic particles [19–25]. The nanoparticles may be further classified into nanosystems depending upon their biochemical composition such as magnetic nanoparticle (MNP), metal oxide nanoparticle, metallic nanoparticle, and bimetallic or alloy nanoparticle. A variety of engineered nanoparticles such as polymeric nanoparticles, carbon nanotubes (CNTs), magnetic nanoparticles, gold (Au) nanoparticles, silver (Ag) nanoparticles, carbon nanoparticles, silica (SiO_2), Cornell dots (C-dots), quantum dots (QDs), and superparamagnetic iron (Fe) oxide nanoparticles (SIONs) uncover the promising applications in biomedical, preclinical/clinical diagnostics and therapy.

In recent years, nanoparticle platforms in conjunction with multimodal imaging technologies have shown tremendous progression, evolving into

new scientific approaches to enhance cancer diagnosis and treatment. Multidisciplinary approaches have been at the forefront to provide a spectrum of novel tools for various biomedical applications such as targeted drug delivery [26–44], biosensors, bioimaging [9], cell labeling [45,46], gene delivery [47–53], photoablation therapy, photodynamic therapy [43,44], and treatment of cancers through heat therapy. This could potentially improve diagnostics, precise targeting, and interventions with added therapeutic efficiency [54–56]. In combination with multiparametric multimodal imaging, iron oxide contrast agents have been used for target-specific molecules [57]; tracking cells [58–60]; and either ex vivo and/or in vivo labeling of various types of cells such as stem cells, red blood cells, and monocytes/macrophages. They are also used to study inflammation [61]; label vaccine [62]; track and deliver drugs [63,64]; probe heterogeneity of pathophysiological status of the region of interest, vasculature [65]; or visualize organs [14,66], in abnormal conditions like cancer, stroke, multiple sclerosis, arteriovenous (AV) malformations, and aneurysms. Nanoparticles frequently vary in their sizes and shapes, and by and large, the transformative power is influenced by their delivery method, surface chemistry, characteristics of the coatings' biomolecular targeting, formation of the protein [9,67], and intracellular targeting [68,69] (Fig. 10.1).

According to their sizes, iron oxide nanoparticles are broadly classified as ultrasmall superparamagnetic particles of iron oxide (USPIOs). Iron oxide nanoparticles with sizes between 50 and 150 nm are categorized as

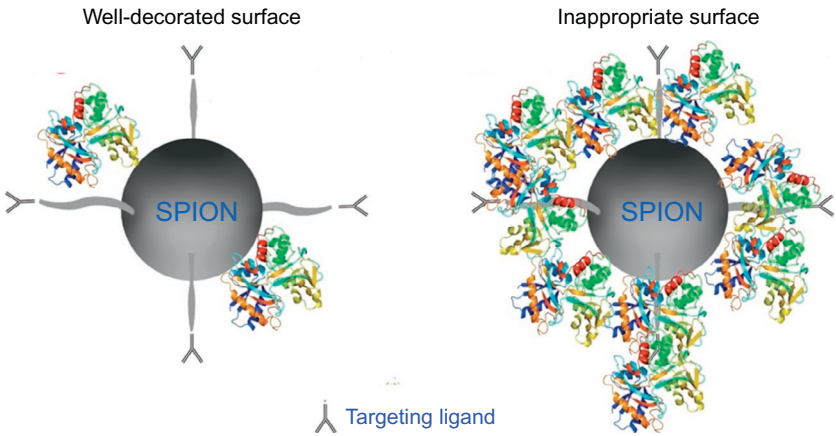

Fig. 10.1 Cartoon showing the important role of surface chemistries in targeted delivery/imaging applications of iron oxide nanoparticles [70].

superparamagnetic iron oxide particles, while those with approximately 1 μm size are termed as micron-sized iron oxide nanoparticles (MSPIOs).

Innovative approaches in theranostics that combine both diagnostics and therapy are currently revolutionizing the field of precision medicine with the next-generation multifunctional nanoparticles as contrast agents for multimodal imaging modalities (Fig. 10.2). In vivo molecular imaging modalities like MRI, PET, SPECT, CT, US, and optical imaging provide larger insights to elucidate these mechanisms at the molecular level. And when these nanoparticles are administrated, they are transduced to overexpress cell differentiation or pathophysiological reactions for a specific period and generate images to visualize the variation in cellular uptake, biodistribution, and clearance over a time frame with distinctive image contrast.

With the state of art imaging capabilities and nanoscale technologies, information technologies have been progressing further to match novel developments of computationally intense algorithms to predict future biomarker candidates. Concurrent uses of hybrid nanomaterials are investigated for its target cell uptake in a time-dependent manner with less or no toxicity and its treatment efficacy. Hybrid nanoparticles often utilize multi-imaging modalities for target interventions using different moieties like fluorophores, near-infrared (NIR) active dyes, carbon nanotubes, nanostars, nanorods, f-block elements, quantum dots, and Cornell dots (C-dots). Larger moieties are frequently functional groups that are hybrid and can be used in

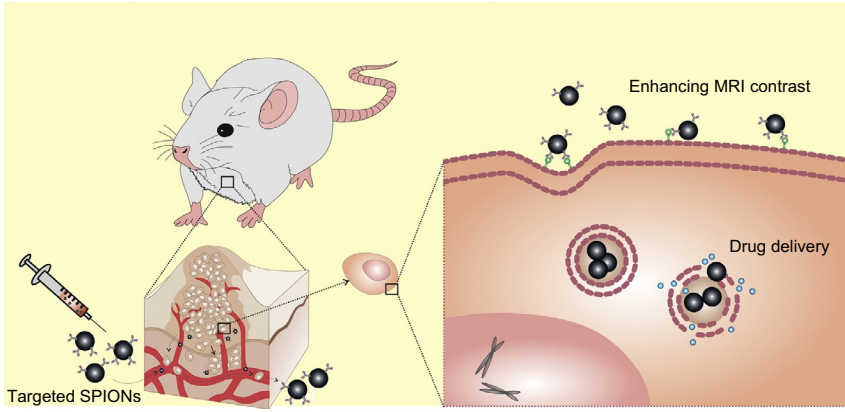

Fig. 10.2 Schematic presentation of active targeting using superparamagnetic iron oxide nanoparticles (SPIONs) and its potential to markedly improve MR imaging and drug delivery. *From Z. Bakhtiary, et al., Targeted superparamagnetic iron oxide nanoparticles for early detection of cancer: possibilities and challenges, Nanomedicine 12 (2016) 287–307, https://doi.org/10.1016/j.nano.2015.10.019.*

conjunction with one or more imaging modalities such as MRI, PET, optical/fluorescent imaging, and ultrasound that can offer greater insights into mechanism of action, enabling better pictures for visualization in addition to the assessment of these hybrid nanoparticles. Among the available nanoparticles that are being used for preclinical and clinical imaging applications, iron oxide nanoparticle (IONP)-based studies have shown great importance due to their unique magnetic properties and compositions. Particularly, the superparamagnetic iron oxide nanoparticles (SPIONs) have generated great attention. Design of nanoparticles may consist of either a core-shell or matrix along with a dendrimer or silica or polymer coating. To facilitate target deliveries, the coating can be attached with target ligands. Hybrid nanoparticle-based studies on quantum dots by combining iron oxide fluorophores are reported for both in vitro and in vivo imaging of cells. Recently, in another breakthrough clinical translation study, hybrid ultrasmall inorganic nanoparticles called Cornell dots (C-dots) for dual-imaging (optical-PET) modality have been reported. Surface modification of nanoparticles can be done through numerous bioconjugates and labeled molecules, and special antibodies can be attached for use in preclinical/clinical and biological applications. More excitingly, a variety of functional nanoparticles such as dendrimers, ligands, liposomes, polymeric micelles, polymeric nanoparticles, mesoporous silica nanoparticles, quantum dots, and C-dots [71–73] are currently being investigated for target therapy [71,73–75]. Biocompatible PEGylated nanoparticles, when coated with amine functional groups, serve as an effective platform for imaging ligands to target and intervene therapeutically. However, another clinically significant promising field is making progress in immunotherapy to study the dynamic interplay between the immune system, disease, and immunotherapy agents.

Image-based contrast-enhancing nanoparticles have fueled further technological developments in smart technologies for unraveling biological events in cellular and molecular imaging. Imaging acquisition and readouts depend on many factors such as signal-to-noise ratio, tumor tissue background, magnetic contrast, emission intensity, size of the NPs, surface functionality, composition of lipid, cell type, uptake, retention, and mitotic cycle interval. This section will analyze the scientific challenges and opportunities faced by this innovative theranostic modality, particularly focusing on the iron oxide nanoparticle interactions with the innate and adaptive immune systems and its biodistribution and tumor targeting.

10.3 IRON OXIDE NANOPARTICLES AND CANCER THERAPY

Magnetic nanoparticles are ideally suited for many biomedical applications owing to their unique magnetic and biochemical properties and high magnetic susceptibility and saturation. Magnetic nanoparticles are widely utilized as theranostic agents for both diagnostics and therapeutic biomedicine applications such as contrast agent for MRI to assess the pathophysiological conditions in the diseased conditions like cancer, target delivery of drugs, and therapeutic monitoring in a time-dependent manner (Fig. 10.3).

Principally, magnetic nanoparticles (MNPs), when subjected to externally applied magnetic force, tend to respond to specific characteristics of the surrounding as they pass through or attach to the region of interest and exhibit a property called longitudinal or transverse relaxation. This property is commonly utilized in magnetic resonance imaging to generate images based on the type of contrast agents used. Longitudinal relativity uses T1 MR contrast agents such as Gd (III) [74,75] or Mn (II) [76,77], whereas

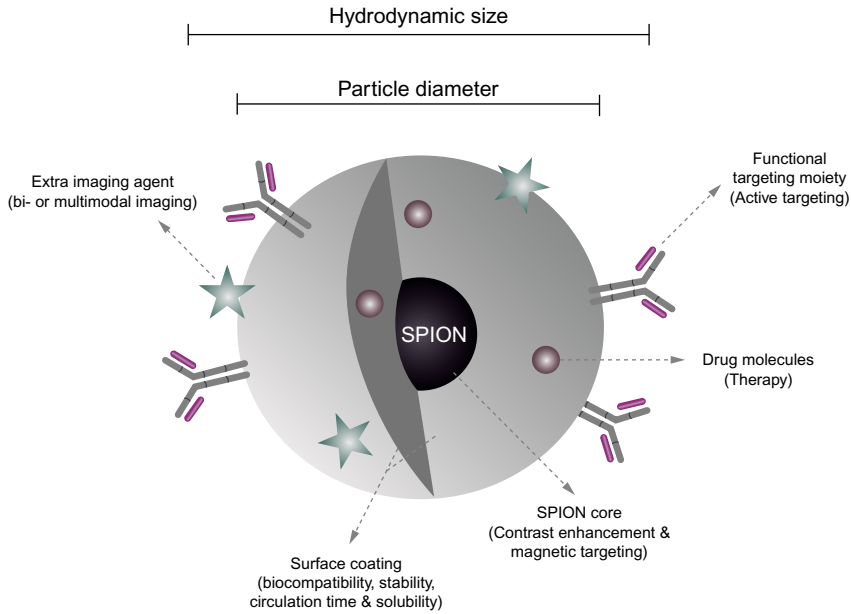

Fig. 10.3 The functions of different components in an iron oxide nanoparticle-based MRI contrast agent.

T2 MR contrast agents utilize agents like magnetic iron oxide nanoparticles (Fe_3O_4 NPs) [22,78–84].

The loss of electrons in iron oxide produces different oxidation states or numbers such as iron (II) oxide (FeO), iron (III) oxide Fe_2O_3, and iron (II and III) oxide Fe_3O_4, which indicates the degree of oxidation. In addition, maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4), Fe_xO_y, FeS_2, Fe_3S_4, and Fe_3O_4-SiO_2 are the most commonly used magnetic materials for various biomedical and imaging applications [18,85–87]. These magnetic nanoparticles are also coated to carry ferrites (often termed as nanocarriers) by chemically combining one or more elements of metals such as copper (Cu), nickel (Ni), cobalt (Co), and magnesium (Mn), along with iron oxide (Fe_2O_4) nanoparticles. These modified nanoparticles produce additional image contrast for better visualization and image quantitation [88] like Nil-xZnxFe_2O_4 nanoparticles, $CoFe_2O$, $MnFe_2O_4$, and superparamagnetic iron oxide nanoparticles (SPIONs) [89]. Superparamagnetic iron oxide nanoparticles are nonpermanent magnets, and they are the most sought after magnetic nanoparticles used in MR imaging. Meanwhile, bimetal nanoparticles that are doped with magnetically susceptible elements such as manganese (Mn), nickel (Ni), and cobalt (Co) are also widely used as tunable magnetic nanovectors or magnetic nanocomposites [89] for preclinical and clinical applications intended for drug delivery. Besides encapsulation with a shell, nanoparticles are often subjected to multifunctionalization and conjugation to their surface chemistry in order to prevent agglomeration and oxidation. The surface modifications of these nanoparticles that are conjugated with antibodies, proteins, enzymes, and anticancer drugs act as a theranostic agent. Manganese iron oxide nanoparticles ($MnFe_2O_4$) have been used both as a contrast agent for diagnostic purposes and magnetic hyperthermia for therapeutic purposes [25,90–99].

Technological innovations have played a significant role in advancing the role of IONP platforms in combination with magnetic resonance engineering and imaging techniques. Michael Garwood and his group have developed a noninvasive, spatially accurate imaging technique called sweep imaging with Fourier transformation (SWIFT) MRI [69]. Safe delivery of alternating magnetic field and quantitative evaluation of IONPs have been widely investigated for various biomedical applications. This novel MRI technique employs ultrashort, T2 MRI sequence to generate series of positive contrast-enhancing images to accurately quantify IONPs in tumor tissue within the clinically achievable therapeutic threshold (0.1–1.0 mg/g tissue) with reduced signal-to-noise ratio. Also, further studies are underway

to optimize SWIFT-IONPs imaging platforms for signal enhancement of other MR techniques such as inversion-recovery spectroscopy and with variable flip angle (VFA). Further studies have reported the sensitivity of SWIFT-based IONPs imaging and quantitation for simultaneous diagnostic assessments of IONP-based biodistribution and heat-based therapy in tumors following intratumor and systemic delivery of iron oxide nanoparticles [69]. Additional correlation studies have observed that the extent of iron oxide nanoparticle aggregation is linked to any decrease in magnetic-field-induced heating. This technique can directly predict local heating and aggregation as well as both the degree of biological characterization and structure of the aggregates, thus providing greater design capabilities for various specific nanoparticle applications in the near future such as controlled release and click chemistry, and inhibit and enhance the transport phenomena of the tracer delivery [18].

Sun C et al. reported a dual-imaging probe for in vivo applications using PEG-mediated iron oxide nanoparticles encapsulated with Cy5.5 near-infrared fluorescent dye after a peptide conjugation with chlorotoxin that has high affinity toward neuroectodermal origin tumors through special synthesis processes. These highly stable, ultrafine well-dispersed iron oxide nanoparticles serve as tumor-targeted drug carriers designed for magnetic resonance imaging and optical fluorescent imaging for tumor-specific accumulation [100].

Furthermore, a multifunctional cancer-targeting theranostic nanoparticle has also been developed by Wang J, Sui M, and Fan W. The study was performed using fluorescent dye indocyanine green (ICG) and in situ growth of iron oxide magnetic nanoparticles on carbon nanoparticles (ICG@MCNPs) for an efficient photothermal therapy (PTT) of tumor. Since these iron oxide nanoparticles are loaded with ICG@MCNPs that enhances the photostability facilitating long-term near-infrared fluorescence (NIRF) imaging, they can be used for greater applications in tumor-targeted nanomedicine [101].

For the first time, Zhaokui Jin et al. proposed a novel concept of MR image-guided and ultrasound-triggered stimulus-responsive release of nitric oxide (NO) for photoacoustic imaging-guided gas therapy for nanomedicine applications. This advanced rattle-type nanocarrier, termed as BNN-type NO-releasing molecule (NORM) of superparamagnetic iron oxide encapsulated with mesoporous silica nanoparticle (BNN6-SPION@hMSN), has the capability for passive tumor targeting and highly efficient and safe NO gas therapy [102].

Since superparamagnetic iron oxide (γ-Fe_2O_3) nanoparticles (SPIONs) act as smart carriers, Wang X et al. proposed tumor-specific ligand folic acid (FA) conjugated onto bovine serum albumin (BSA-SPIONs) that were subsequently labeled with fluorescein isothiocyanate (FITC) to identify potent cellular uptake and intracellular visualization. These fluorescent magnetic albumin nanoparticles (FITC-FA-BSA-SPIO NPs) were fabricated as a promising dual-modality target-specific MRI contrast agent and fluorescent imaging for human brain tumor cells [103].

Similar studies by Wang S et al. have investigated multifunctional nanocarriers based on superparamagnetic iron oxide nanoparticles (SPIONs) coated with reduction-responsive SPIO/doxorubicin (DOX)-loaded poly(ethylene glycol) monomethyl ether (PEG)ylated polymeric lipid vesicles (SPIO-DOX-PPLVs) for theranostic proposes. These magnetic nanosystems, having size structures around 80 nm, possess excellent targeting properties with increasing T2 relaxivity in the range of $r2 = 213.82\ mM^{-1}\ s^{-1}$ and antitumor activity. The polymer matrices encapsulating the SPIONs function as an excellent targeted contrast T2-weighted tumor agent for MR and delivery of antitumor drug [104].

Also, a superparamagnetic iron oxide nanoparticle (SPION) fabricated with DNA-RNA hybridized aptamer (A10-3-J1) and doxorubicin (SPION-APT-DOX) was designed to target prostate-specific membrane antigen (PSMA)-specific prostate cancer cells. The main advantage of this aptamer conjugated SPION is that it inhibits nonspecific uptake of doxorubicin to nontarget cells, thereby enhancing targeted endocytic uptake especially to develop more specific therapies without damaging the normal healthy cells [105]. A dual-targeting Fe_3O_4 nanoparticle with innate innoxious hyaluronic acid (HA) and transferrin (Tf) was developed at an ambient temperature after a facile procedure. Tf was attached following a one-step coprecipitation method to yield a dual-targeting MR imaging probe. This Fe3O4-HA-Tf nanoprobe was tested for in vitro and in vivo assays using Hela cells, which are shown to overexpress both CD44 and transferrin receptors. The results suggested excellent biocompatibility with increasing ability to target tumor cells. This human-inherent component that consists of molecules has found greater potential utility in the clinical diagnosis of tumors [106]. Su YL et al. demonstrated the usage of magnetic field (MF)-induced perfluorohexane (PFH) in the form of burst-like drug release as a deep tumor-penetrating drug-delivery agent. These mesoporous iron oxide nanoparticles (MIONs) were capped with lactoferrin (Lf) biogate and through a payload of perfluorohexane (PFH) and paclitaxel (PTX).

Biocompatible PFH was selected due to its hydrophobicity and favorable phase transition temperature (56°C) [107]. This is based on the principle that when the Lf-MIONs/PTX-PFH nanoparticle is subjected to the onset of the short pulse of magnetic field, it produces heat. This, in turn, increases the local pressure to rupture the three-dimensional tumor spheroids in vitro, and the effect of gasifying enhances the drug release and penetration of the targeted nanocarrier for thermochemotherapy of tumors [107].

A novel tumor-targeted drug-delivery system based on rapamycin (Rapa) has been developed. As a curative effect of the drug, normal-cell damage is reduced. Also, theranostic agents are delivered to the tumor cells. This spherical-in-shape antitumor drug with a size of 30 ± 2 nm when loaded with rapamycin and magnetic iron oxide (Fe_3O_4) conjugated with carboxymethylchitosan (CMCS) nanoparticles (Fe_3O_4/CMCS-Rapa NPs) exhibited a pattern of biphasic drug release with initial burst release and later continued with sustained release. These Fe_3O_4/CMCS-Rapa nanoparticles possess good loading efficiency of the Rapa drug ($6.32\pm0.34\%$) and permit a saturated magnetization in the range of 67.1 emu/g. The study results demonstrated higher cytotoxicity to a human hepatocarcinoma cell line (HepG2) and lower cytotoxicity to a liver cell line (LO2) when compared with the native Rapa drug [108].

In an effort to advance gene therapy, nanovector-engineered iron oxide nanoparticles were modified for the delivery of surfactant-free lipopolymersomes (LPPs) by a 30- to 40-fold increase in cancer cell uptake that further enhances in vivo transfection efficacy by supporting the endosomal escape of gene molecules. In this study, Hu SH et al. reported a combined use of an external magnetic field trigger to promote folate-receptor-mediated endocytosis on the surface of cancer cells through magnetic nanoparticles that were capped with folic acid (FA). These lipid-stabilized double emulsions were capable of promoting transfection efficiency and delivering gene molecules to the target cells through magnetically guided methods synergistically.

Recently, inhalable superparamagnetic iron oxide nanoparticles were also investigated for targeted hyperthermia planned tumor ablation employing an alternating magnetic field. These inhalable SPIONs were synthesized for enhanced EGFR target and tumor retention and magnetic-hyperthermia-mediated antitumor efficacy. This study showed relatively large in vivo lung tumor growth inhibition and may be a potential candidate for enhanced permeability and retention (EPR)-based anticancer treatments [109].

10.4 CONCLUSION

This review chapter highlights the investigating mechanism of iron oxide nanoparticles with multifunctional capabilities and concomitant multimodal imaging methods to precisely target delivery systems for cancer treatments. The multidisciplinary interface of bionanomaterials and nanomedicine further widens the development of iron oxide nanoparticles to deliver drugs, at controlled rates for prolonged or intermittent periods. Often, technology can be used to regulate the release rates by triggering either enzymatically, ultrasonically, or magnetically. Futuristic opportunities and challenges include the design of novel biodegradable nanoparticles that will in due course be absorbed by the body itself and modeling of in vivo conditions to better understand their interactions with the blood system and the ability to traverse complex biological barriers such as the blood-brain barrier during delivery of drugs across complex barriers.

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