Chapter 2

Recent Advances in Bioimaging for Cancer Research

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Additional information is available at the end of the chapter

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Abstract

Molecular imaging techniques as well as nanoparticle applicable to molecular imaging are being explored to improve the cancer detection accuracy, which help to manage efficiently at the early stage. Among the various imaging technologies, optical imaging is a highly sensitive detection technique that allows direct observation of specific molecular events, biological pathways, and disease processes in real time through imaging probes that emit light in a range of wavelengths. Recently, nanoparticles have provided significant progresses that can be simultaneously used for cancer diagnosis and therapy (cancer theranostics). Theranostics aims to provide "image-guided cancer therapy," by integrating therapeutic and imaging agents in a single platform. In addition, molecular imaging techniques facilitate "image-guided surgery" enabling maximization of tumor excision and minimization of side effects. The optical signals generated by fluorescence nanoparticles offer the possibility to distinguish tumor sites and normal tissues during surgery by real-time guidance, thereby increasing the long-term patient survival. These techniques will considerably contribute to reducing cancer recurrence and developing more effective cures. In this chapter, we will introduce diverse research on nanomaterials-based optical imaging for effective cancer therapy.

Keywords: molecular imaging, optical imaging, nanoprobe, cancer diagnosis, imaging-guided therapy, imaging-guided surgery

1. Introduction

Cancer is one of the leading causes of death. So many researchers have made great efforts to improve cancer management [1]. An early cancer diagnosis provides the most efficient and effective management of cancer treatment with the use of surgical methods or chemotherapeutic agents. Therefore, techniques for detecting cancer at early stages have been developed to improve the detection accuracy. Molecular imaging techniques have undergone explosive growth over the past several decades and are important tools for cancer diagnosis and prognosis

in the clinic; they include positron emission tomography (PET), computed tomography (CT), magnetic resonance (MR) imaging, and optical imaging [2–4]. Molecular imaging techniques can identify the cancer mass on the basis of its physical properties, which may have major benefits for personalized diagnosis and for the prediction and monitoring of the response to therapy. Many researchers have made efforts to develop diverse imaging probes or contrast agents, thereby enabling the visualization of cellular function and the characterization and measurement of molecular processes in living organisms at the cellular and molecular levels without perturbing them. Such tools can help obtain more accurate information about early-stage cancer using molecular imaging [4]. Among the molecular imaging tools, optical imaging, which includes fluorescence and bioluminescent imaging, can provide particularly highly sensitive detection by using the various wavelengths emitted by fluorescent nanoparticles. In the UV and visible regions, light does not deeply penetrate into tissues, because it is easily absorbed and scattered by endogenous biomolecules (e.g., water and hemoglobin), and tissues generate strong auto-fluorescence [4]. However, light in the near-infrared (NIR) region (~650–900 nm) is minimally absorbed in living tissues and can penetrate more deeply, to a depth of several centimeters, with high signal-to-noise ratios (SNRs) [2]. The development of specific, sensitive, and targeted imaging probes is required for the success of optical imaging techniques in cancer diagnosis. Recently, nanomaterial-based optical imaging probes have been used extensively to non-invasively monitor the target biomolecules or biological pathways for cancer diagnosis and therapy compared with single molecule-based imaging agents. Fluorescent proteins and organic dyes are conventionally used to label cells and subcellular targets due to their small size, good biocompatibility, and water dispersibility. However, fluorescent nanomaterials such as quantum dots (QDs), gold nanoparticles, up-conversion nanocrystals, and silicon nanoparticles have shown several distinct advantages compared to fluorescent proteins and organic dyes [5–9]. These advantages include high resistance to photobleaching (photostability) and high quantum yields (QY), thus enabling the acquisition of optimal information of biological interest with high sensitivity in both *in vitro* and *in vivo* models [9]. In addition, nanomaterials (or nanoparticles) have the advantage that they can be easily modified with different molecules and delivered to the tumor along blood vessels with

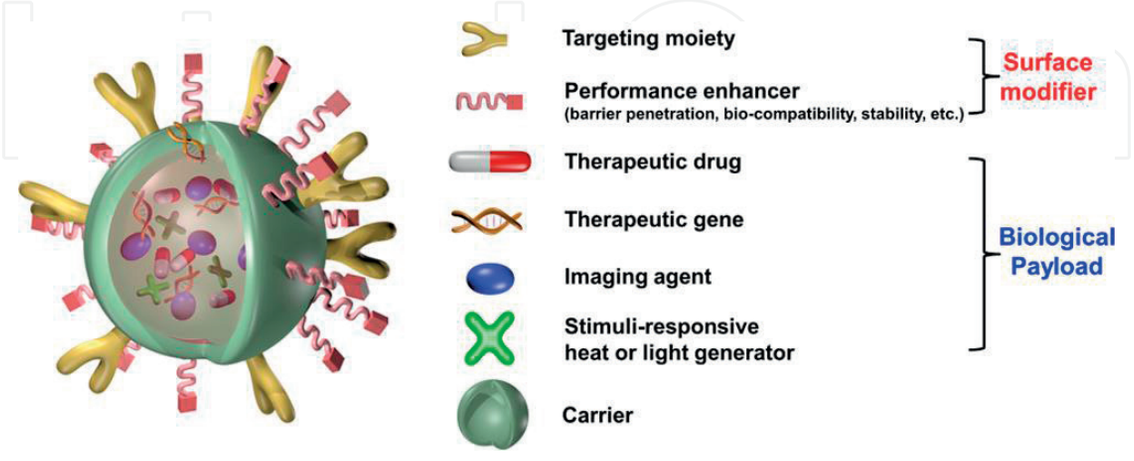

Figure 1. Schematic illustration of a multifunctional nanocomposite. Reproduced from Ref. [12] with permission of ACS Publications.

immune systems [10–13]. In this chapter, we explain the benefits of optical imaging and the importance of nanomaterial-based imaging agents for effective cancer therapy. We will focus on research on using nanomaterials as optical imaging agents and their diverse applications (**Figure 1**).

2. Passive and active targeting for cancer imaging

2.1. Passive targeting

Various nanoparticle systems are being explored for their potential use in bioimaging for cancer diagnosis or treatment because of their unique properties, including their large surface-to-volume ratio, high biocompatibility, facile surface modification, and overall structural robustness. In addition, they have unique optical, magnetic, and electron properties, which make them ideal candidates for signal generation and transduction in the development of sensing systems [5–8, 12, 14–20]. Moreover, some nano-sized materials exhibit unique physical properties, such as a proper size, surface charge, stability, shape, and hydrophilicity, which can aid their effective delivery to the desired site. The delivery of nano-sized agents is affected by the enhanced permeability and retention (EPR) effect, which is a unique property of solid tumors that is related to their anatomical and pathological differences from normal tissues. Unlike normal tissues, when tumor tissue produces neovascularization, it contains a discontinuous or absent basement membrane, making it "leaky." Therefore, the pore sizes of the blood vessels in most peripheral human tumors are hundreds of nanometers in diameter. This EPR effect leads to the passive accumulation of large molecules and small particles in tumor tissues due to the cut-off size of the leaky vasculature and retention with long circulation times, which is called passive targeting [21–26]. For successful bioimaging via passive targeting, both a size ranging from 100 to 200 nm in diameter and a prolonged circulation half-life in the blood with biocompatibility are required. Hydrophilic materials such as poly(ethylene glycol) (PEG) have been extensively investigated as effective ways to provide hydrophilic "stealth" properties, resulting in both the inhibition of plasma protein (opsonin) absorption and decreased recognition by the mononuclear phagocytic system (MPS) in the reticuloendothelial system (RES), such as the liver and spleen, thus producing longer circulation times (**Figure 2**) [27–29].

In addition, positively charged (cationic) nanoparticles can easily enhance endocytosis or phagocytosis for cell labeling via electrostatic interactions with the negatively charged cellular membrane. Among bio-imaging techniques, well-tailored superparamagnetic nanocrystals are of great interest for cancer detection via magnetic resonance (MR) imaging due to their high sensitivity and specificity due to the nanoeffect. Lim et al. [30–32] reported the successful fabrication of various types of water-soluble PEGylated magnetic complexes for magnetism-related biomedical applications and demonstrated their potential as highly efficient MRI imaging agents. Fluorescence and optical imaging techniques are important tools for *in vivo* and cellular imaging, and they can provide vital information for cancer diagnosis and therapy in its early stages. In particular, for the fluorescence wavelength, near-infrared (NIR) light is

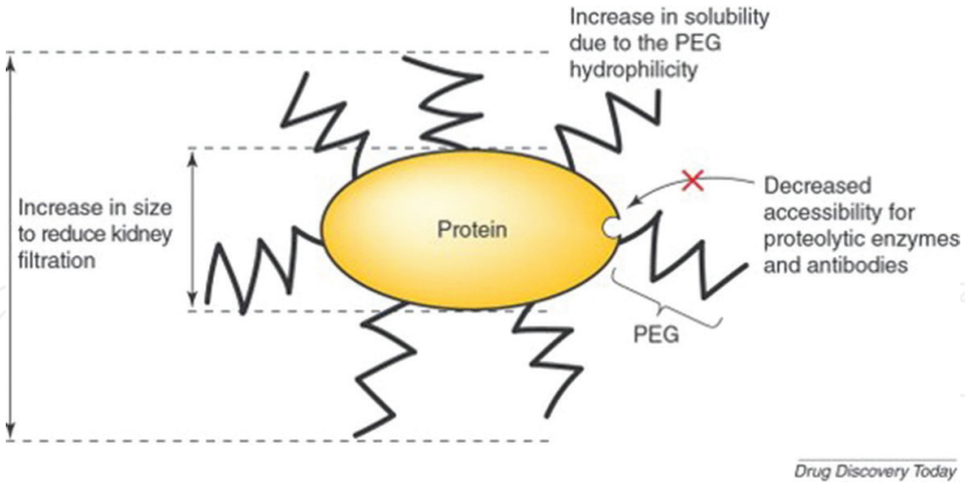

Figure 2. Main advantages of the PEGylated proteins. PEG is a shielding the protein surface from degradation agents by steric hindrance. Moreover, the increased size of the conjugate decreases the kidney clearance of the PEGylated protein. Reproduced from Ref. [27] with permission of Elsevier.

preferred for tissue and *in vivo* imaging compared to visible light because of its minimal damage to the tissue, which allows deep tissue penetration, and low auto-fluorescence interference due to the reduced scattering of long wavelength photons [9].

2.2. Active targeting

Active targeting, is also called as ligand-mediated targeting, involves utilizing targeting moieties that are anchored on the surface of nanoparticles and form strong interactions with a particular cell surface marker (e.g., EGFR, HER2/neu, transferrin, CD44) of the target cancer (**Figure 3**) [33, 34].

Targeting moieties, such as antibodies, peptides (Arg-Glyc-Asp (RGD)), nucleic acids (aptamers), and polysaccharides (hyaluronan, dextran), lead to enhanced selective delivery and uptake in the target cells, tissues, organs, or subcellular domains and minimize uptake by the RES system [34–53]. Active tumor targeting is more efficient and specific than passive targeting, and can facilitate early cancer detection. In particular, active tumor-targeted imaging can quantify the target expression through molecular imaging, so it is an indispensable tool in diagnosis and disease management. For example, for the selective detection of tumors expressing a high level of epidermal growth factor receptors (EGFR), anti-EGFR antibody-modified nanoparticles are widely used as imaging agents for MR, CT, and optical imaging. CD44 is a cell surface glycoprotein that is overexpressed in breast cancer and gastric cancer stem cells and is associated with cancer growth, migration, invasion, and angiogenesis. Hyaluronan (HA), which is an immune–neutral polysaccharide, forms a specific interaction with CD44. Lim et al. [50, 51] developed a hyaluronan-modified magnetic nanoprobe for detecting CD44-overexpressing breast cancer via MR imaging, which showed superior targeting efficiency with MR sensitivity in *in vitro* and *in vivo* studies. Angiogenesis appears to be one of the most crucial steps in tumor translation to the metastatic form, in which it is

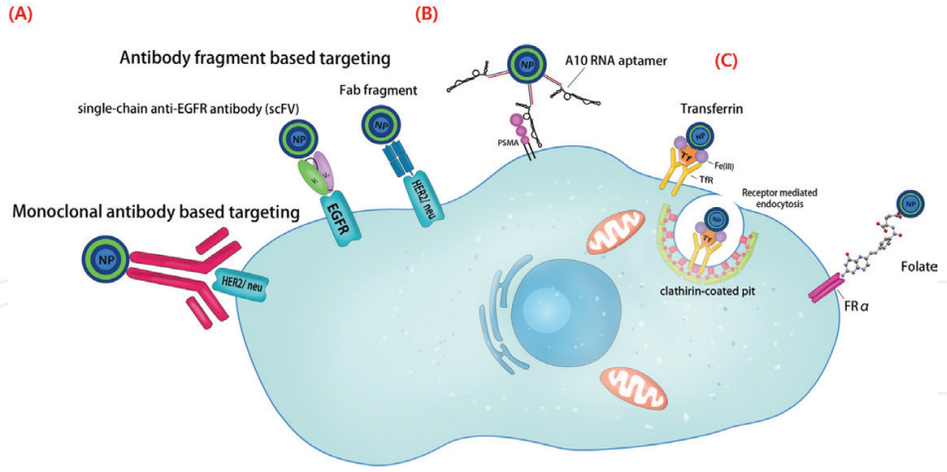

Figure 3. A schematic illustration showing methods used for active targeting of nanoparticles. (A) Antibody-based targeting, (B) Aptamer-based targeting, and (C) Ligand-based targeting of nanoparticels. Reproduced from Ref. [34] with permission of Springer.

capable of spreading to other parts of the body by degrading the basement membrane and forming a new vascular structure. During angiogenesis, a variety of proangiogenic factors is secreted by tumor cells, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), interleukin-8 (IL-8), and integrin $\alpha_v\beta_3$. Targeted-molecular imaging of vascular or angiogenesis can provide accurate anatomic details for effective cancer management. Aptamers (Apt) are short nucleic acid molecules that can bind to target antigens with high affinity and specificity. To understand neovascularization and angiogenesis in cancer, $Apt_{\alpha v\beta 3}$-conjugated magnetic nanoparticles ($Apt_{\alpha v\beta 3}$-MNPs) have been developed to enable the precise detection of integrin-expressing cancer cells using MRI imaging. This work demonstrated that $Apt_{\alpha v\beta 3}$-MNPs have the potential to be used for accurate tumor diagnosis [52]. In addition, vascular endothelial growth factor (VEGF121)/rGel modified MRI imaging agents were developed to obtain sensitive angiogenesis imaging of orthotopic bladder tumors that showed the development of a clear neoangiogenic vascular distribution [53]. The tumor microenvironment plays a critical role in tumor initiation, progression, metastasis, and resistance to therapy [54–61]. The microenvironment differs from that of normal tissues because of the dynamic network within normal tissues, including blood and lymphatic vessels, extracellular matrix proteins, and both enzyme and immune components. These unique characteristics lead to a matrix remodeling (e.g., up-regulation of matrix proteins and activation of specific proteases), a deficiency of oxygen and other nutrients, a decreased pH (low pH), hypoxia and increased amounts of reactive oxygen species (ROS) [57]. The changes in the physiological characteristics of tumor microenvironments are consistent, regardless of the type of cancer, so it is possible to use these as a universal indicator for cancer detection. Vesicular pH plays a pivotal role in cell metabolism processes, such as proliferation and apoptosis. Choi et al. [58] developed a colorimetric redox-polyaniline nanoindicator to simply detect and quantify a broader biogenic pH range with superior sensitivity by employing one-dimensional turn-on of the FRET signal (**Figure 4**). They fabricated polyaniline-based

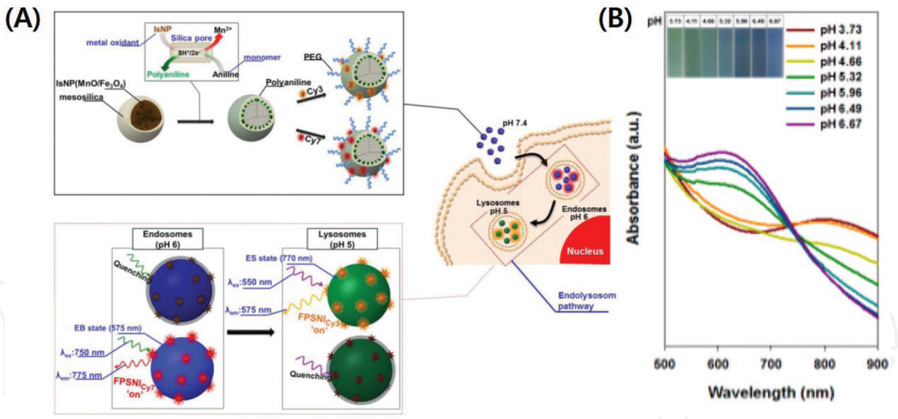

Figure 4. (A) Schematic illustration of organic nanoindicator based on polyaniline nanoparticle for the detection of endolysosomal compartments. Synthesis steps of nanoindicator based on polyaniline in mesosilica template when using heterometal nanoparticle (IsNP) as oxidant. Emission of FPSNICy7 appears at endosomes. While migrating from endosomes to lysosomes, transition state of polyaniline transferred to emeraldine salt state due to the increment of proton concentration. The emission of FPSNICy3 gradually appears at lysosomes. (B) Redox switching property and sensitivity of PSNI from pH 3.95 to 7.23. Reproduced from Ref. [58] with permission of Springer.

nanoprobes that exhibited convertible transition states according to the proton concentration as an *in situ* indicator of the vesicular transport pH [58].

The tumor pH is usually more acidic than that of normal tissues due to increased aerobic glycolysis, which is called the Warburg effect (tumor have a pH of 6.2–6.9, and normal tissues have a pH of 7.4) [62, 63]. This can promote tumor metastasis by generating an invasive environment for tearing down the extracellular matrix and for tissue remodeling. Many studies have reported signal "off–on" imaging agents activated by pH, such as fluorescence probes and MRI contrast agents that target the acidic pH conditions of tumors for tumor imaging [12, 13, 59]. Kim et al. [59] have developed a pH-responsive T1 (which is the recovery of magnetization along the longitudinal axis) contrast agent for MR imaging. Core–shell MnO@ Mn_3O_4 urchin-shaped nanoparticles are synthesized via an anisotropic etching process. The manganese ions released from the MnO phase in the low-pH sites within tumor cells lead to an enhanced T1 contrast image for the entire tumor mass. In addition, specific stromal cell-derived proteases, such as matrix metalloproteases (MMP), matrix cysteine cathepsins, and serine proteases, are overexpressed in primary tumors. These proteases induce the epithelial-to-mesenchymal transition (EMT) and promote invasion and metastasis by degrading the extracellular membrane. Molecular imaging of the activity of proteases has the potential to determine tumor malignancy, guide the development of diagnostic tools, and evaluate the efficacy of treatment (**Figure 5(A)**) [60]. MMPs are the most prominent family of proteases associated with tumorigenesis. Their expression and activity are highly enhanced in many types of human cancer and are strongly implicated in advanced cancer states. Tumor microenvironment-targeted molecular imaging has the potential to provide clinically significant progress. Emerging evidence suggests that microRNAs can also function as a diagnostic biomarker for human cancers because they can act as tumor suppressor genes or oncogenes. Imaging the intracellular distribution of specific miRNAs should provide insight into the mechanisms of metastasis and invasion. Kim et al. [61] reported smart nanoprobes,

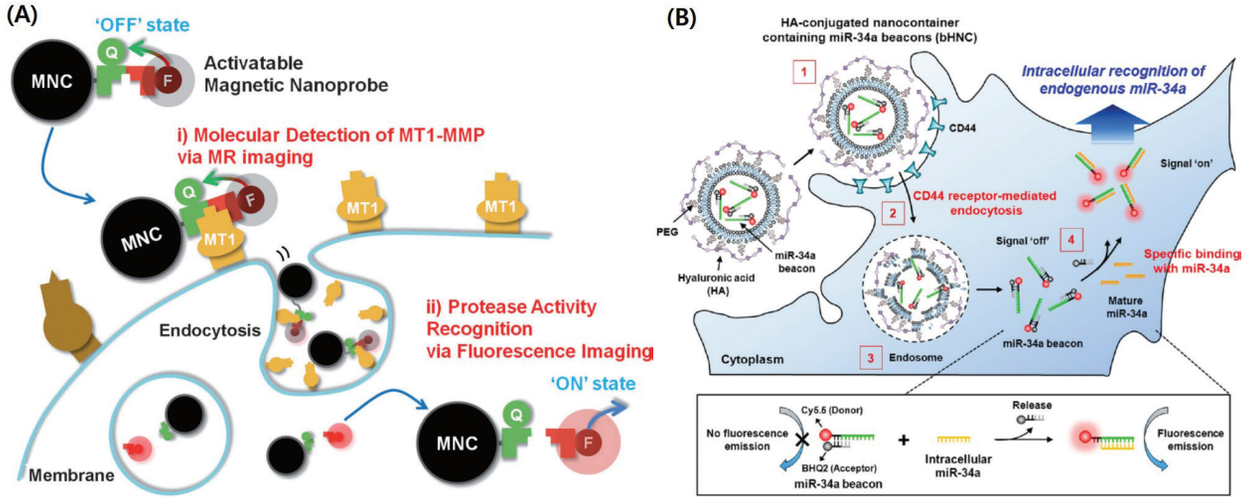

Figure 5. (A) Schematic illustration of the dual imaging process of anchored proteinase-targetable optomagentic nanoprobes with activatable fluorogenic peptides (MNC-ActFP). Reproduced from Ref. [60] with permission of Wiley-VCH. (B) Schematic illustration of miR-34a beacon delivery system for targeted intracellular recognition of miR-34a based on Hyaluronic acid (HA)-coated nanocontainers that encapsulate the miR-34a beacons (bHNCs). Reproduced from Ref. [61] with permission of ACS Publications.

i.e., hyaluronic acid (HA)-based nanocontainers containing miRNA-34a beacons (bHNCs), for the intracellular recognition of miRNA-34a levels in metastatic breast cancer cells. They confirmed the microRNA-34a expression levels through *in vitro* and *in vivo* optical imaging using bHNCs (**Figure 5(B)**) [61].

3. Multimodal imaging for cancer imaging

Current imaging techniques play an important role in enabling the early detection of several diseases, including cancer, due to their ability to locate tumors and assess the tumor activity. The characteristics of various imaging modalities are briefly summarized (**Table 1**) [7, 64]. However, these techniques are insufficient to provide reliable and accurate information at the disease site, due to their low sensitivity or limits in their spatial resolution (**Table 1**).

Computed tomography (CT) is useful for tumor staging but offers poor soft tissue contrast, with resulting poor sensitivity and specificity in screening. Magnetic resonance imaging (MRI) offers excellent contrast without ionizing radiation but has temporal and financial needs that are likely inconsistent with high-throughput screening. Positron emission tomography (PET), which has very high sensitivity, can investigate various molecular and biochemical properties but is more suitable for monitoring the response to therapy than for detecting early lesions due to its limited spatial resolution. Therefore, multimodal imaging, i.e., the integration of two or more imaging techniques in a single examination, should offer the synergistic advantages of each to provide accurate information for tumor diagnosis such as high spatial resolution, soft tissue contrast, and biological information on the molecular level with high sensitivity [46, 65–73]. Recently, various types of hybrid nanoparticles have

been used for multimodal imaging by combining the strengths of individual components into single nano-structured systems. Multimodal imaging probes enable both magnetic and optical imaging to provide great benefits for *in vivo* disease diagnosis and the *in situ* monitoring of living cells. In addition, it is reported that MR/CT multimodal nanoprobes can provide complementary information for tumor-associated blood vessels and the tumor microenvironment [71]. Uniformly sized tantalum oxide nanoparticles were synthesized using a microemulsion method and were modified using various silane derivatives, such as polyethylene glycol (PEG) and fluorescent dye molecules, through simple *in situ* sol-gel reaction. These nanoparticles exhibited remarkable performances in *in vivo* simultaneous fluorescence imaging as well as X-ray CT angiography and bimodal image-guided lymph node mapping [72].

Lim et al. [73] developed fluorescent magnetic nanoprobes to acquire biological information at different object levels, i.e., *in vivo* detection and *ex vivo* validation, for characterizing tumor angiogenesis, in which magnetic nanocrystals are encapsulated by the fluorescent amphiphilic polymer (**Figure 6**). Additionally, targeted multimodal imaging systems by modifying targeting moieties to increase the selective accumulation at the disease site has shown promising results. In this case, several factors should be considered, including the appropriate choice of a targeting moiety and its conjugation method. Yang et al. [49] developed

Modality	Energy source	Depth	Temporal resolution	Advantage	Disadvantage
Optical imaging	Visible light or near-infrared	<1 cm	Seconds to minutes	Noninvasiveness, no harmful effect by nonionizing radiation	Relatively low spatial resolution
MR imaging	Radiofrequency magnetic field	No limit	Minutes to hours	Noninvasiveness, high spatial resolution	Relative low sensitivity, long scan and post-processing time, mass quantity of probe may be needed
PET imaging	High-energy γ rays	No limit	10 s to minutes	Noninvasiveness, high sensitivity	Exposure to ionizing radiation, relatively low spatial resolution
Ultrasound imaging	High-frequency sound	mm to cm	Second to minutes	Noninvasiveness, real time, low cost, no harmful effects by nonionizing radiation	Limited spatial resolution, unsuitable for examination of digestive organs and bone
CT imaging	X-ray	No limit	Minutes	Noninvasiveness, high contrast resolution	Relatively high dose of ionizing radiation, limited soft tissue resolution, exposure to ionizing radiation

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Table 1. Characteristics of imaging modalities.

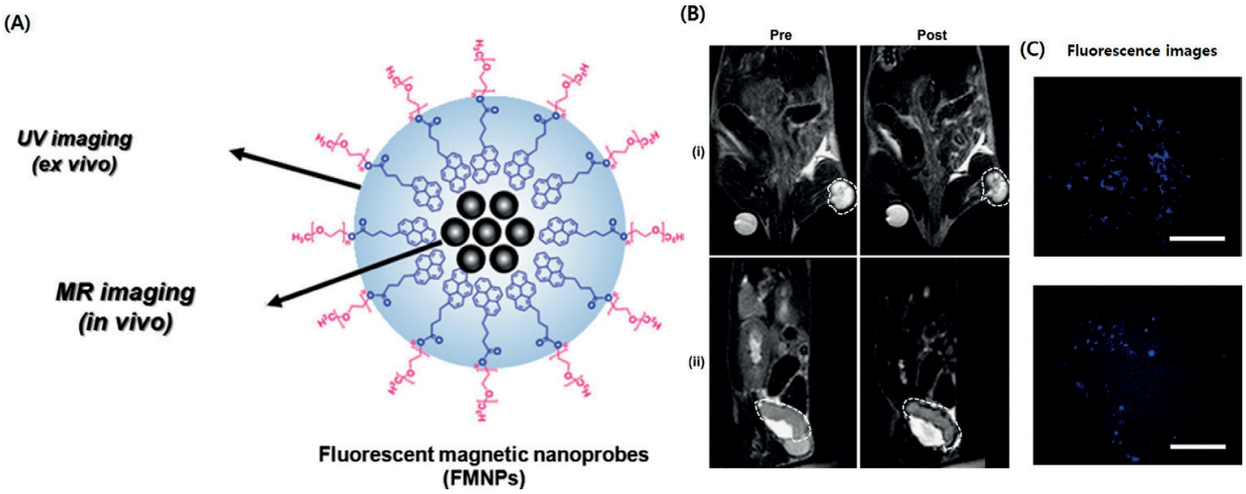

Figure 6. (A) Illustration of simultaneously self-assembled fluorescent magnetic nanoprobes (FMNPs) as multimodal biomedical imaging probes. (B) MR images of tumor-bearing mice after injection of the FMNPs (i: xenograft tumor model and ii: orthotopic bladder tumor model) and (C) fluorescence images of their excised tumor slides, respectively. Reproduced from Ref. [73] with permission of Elsevier.

Cetuximab-conjugated fluorescent magnetic nanohybrids (CET-FMNHs) that served as effective agents for both magnetic resonance (MR) and fluorescence optical imaging of human epithelial cancer.

4. Optical-imaging-based cancer therapy

4.1. Optical imaging in drug delivery (Theranostics)

Recently, nanoparticles have provided significant progress in cancer theranostics due to their unique physicochemical properties, in which both diagnosis and therapeutic functions can be achieved simultaneously. Theranostics aims to provide image-guided cancer therapy by integrating imaging and therapy, which are particularly interesting fields in Nanomedicine [12]. Theranostic nanoparticles comprise at least three components: (i) the biological payload, (ii) the carrier, and (iii) surface modifiers (**Figure 1**) [74–93]. Biological payloads include imaging agents and therapeutic agents. Therefore, they can allow the simultaneous delivery of therapeutic agents to the tumor site and real-time tracking of their biodistribution *in vivo*. Optical imaging has advantages in theranostics because it allows the non-invasive monitoring of the progression of diseases and therapy [84]. For example, Misra et al. [85] synthesized blue-light-emitting ZnO quantum dots combined with biodegradable chitosan (N-acetylglucosamine) for tumor-targeted drug delivery (a ZnO-QD-chitosan-folate carrier), which was loaded with an anti-cancer drug (DOX). The DOX-loaded ZnO-QD-chitosan-folate carrier exhibited highly stable QDs because of its hydrophilicity and the cationic charge of chitosan as well as a rapid drug release profile with a controlled release.

Ryu et al. [86–89] developed chitosan-based nanoparticles (CNPs) that were labeled with Cy 5.5 for optical imaging and encapsulated with paclitaxel (PTX) as an anticancer drug

(PTX-Cy5.5-CNP) (**Figure 7**). They confirmed that the PTX-Cy5.5-CNP was effectively delivered to the tumor sites by optical imaging and that it showed enhanced therapeutic efficacy in tumor tissues while minimizing its toxicity to normal tissues. Smart theranostic nanosystems that respond to environmental changes (e.g., pH) have been designed for controlled drug release, low drug loss and low side effects [90–92]. Wu et al. prepared nanogels via the *in situ* immobilization of CdSe quantum dots (QDs) in the interior of pH and temperature-responsive hydroxypropylcellulose-poly(acrylic acid) (HPC-PAA) semi-interpenetrating (semi-IPN) polymer networks (HPC-PAA-CdSe hybrid nanogels). These nanogels demonstrated potential as excellent drug carriers, providing a high drug loading capacity for TMZ as a model anticancer drug and offering the possibility of pH-regulated drug delivery [93]. Jang et al. [94] used nanovesicles containing poly(L-lysine-graft-imidazole) (PLI)/miR complexes (NVs/miR) to systemically deliver miR-34a for CD44 expression-based cancer therapy (**Figure 8**).

In this system, the PLI acts to deliver miRNA to the site of action via the buffering effect of the imidazole residues under endosomal pH. This systemic delivery of miR-34a using our NVs shows the most favorable delivery efficiency, a significant suppression of CD44 expression, and increased apoptosis in the *in vivo* models [94]. In optical imaging, fluorophores, such as fluorescent dyes, bioluminescent proteins and fluorescent proteins, are widely used to monitor molecular events. However, they are easily susceptible to photobleaching. Fluorescent nanoparticles (e.g., quantum dots, upconversion nanoparticles) were developed that complement the weakness of fluorophores; however, they also exhibited potential toxicity [95]. Among various nanoparticles, gold nanoparticles are the most widely used in the biomedical field because of their advantageous properties such as biocompatibility and facile modification [96–102]. According to their size, shape, and structure, they also have controllable surface plasmon resonance (SPR). Among gold nanoparticles, rod-shaped gold nanoparticles

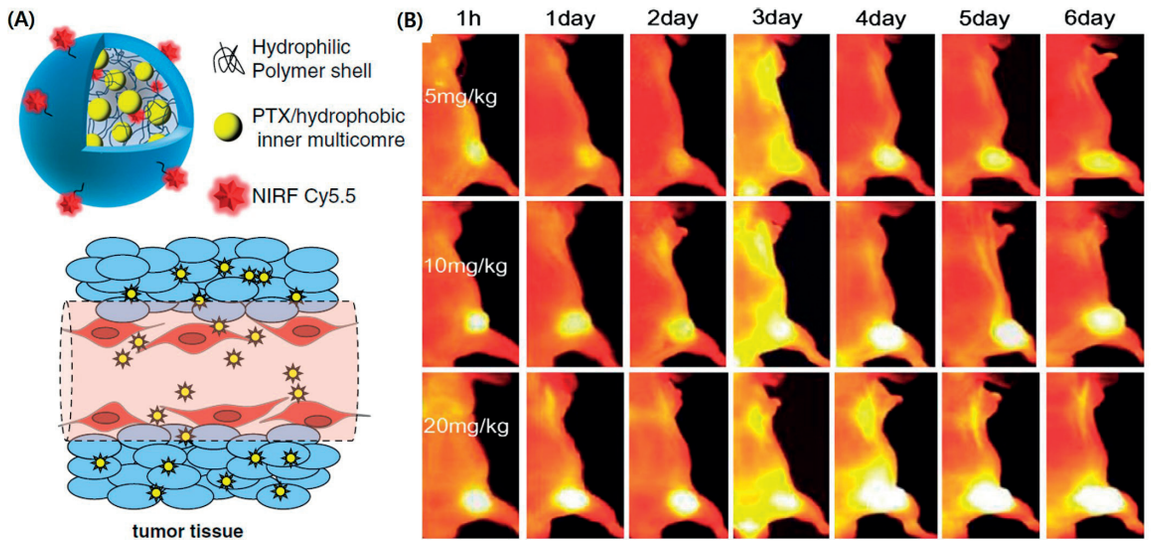

Figure 7. Theragnostic chitosan-based nanoparticles (CNPs) for cancer imaging and chemotherapy. (A) Conceptual description of theragnostic nanoparticles labeled with Cy5.5 for imaging and encapsulated with PTX for cancer therapy (PTX–Cy5.5–CNP). (B) *In vivo* images of the tumor-bearing mice treated with PTX–Cy5.5–CNP of different drug concentrations (5, 10, and 20 mg/kg) every third day. Reproduced from Ref. [88] with permission of Elsevier.

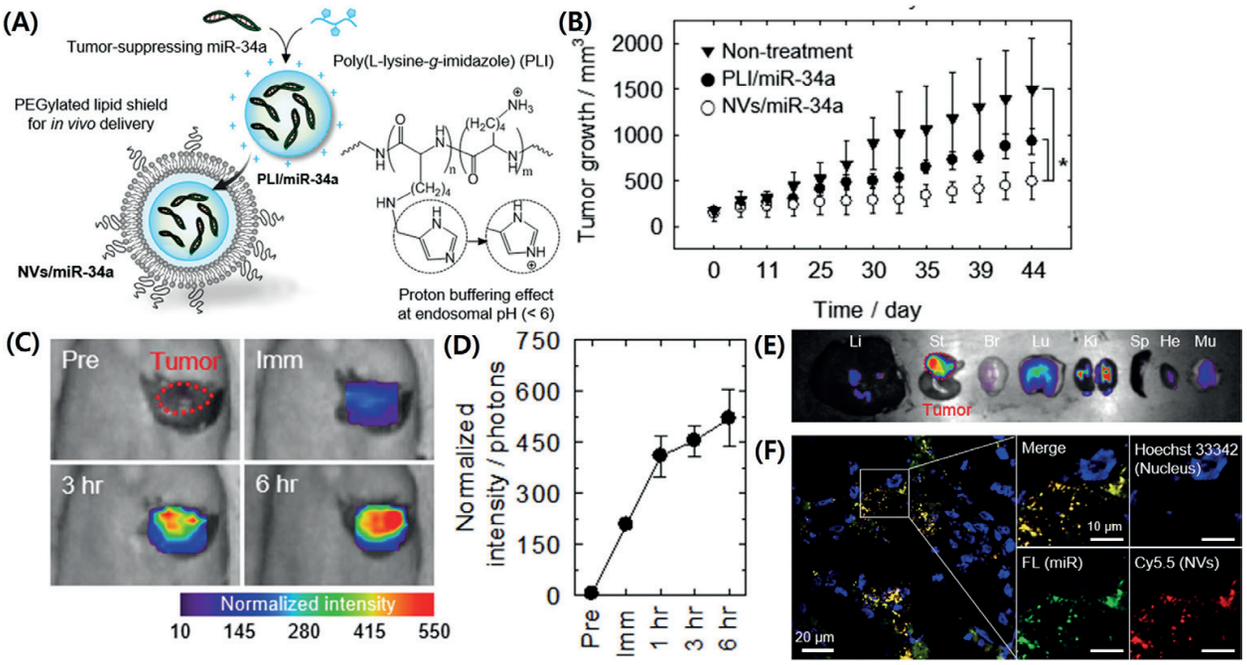

Figure 8. (A) Schematic illustration and characterization of nanovesicles containing PLI/miR complexes (NVs/miR) that proton buffering promoted by protonation of a pH-responsive cationic polymer, poly(L-lysine-graft-imidazole (PLI), at endosomal pH, (B) *in vivo* anti-tumor effects induced by NVs/miR-34a, (C) I optical images of Cy5.5-labeled NVs containing PLI/fluorescein-labeled miR (Cy5.5-NVs/FL-miR) in an MKN-74 gastric subcutaneous xenograft model after intravenous injection of Cy5.5-NVs/FL-miR at various time intervals (pre-injection, 0, 3, and 6 h) and (D) its photon counts from the tumor regions after injection of Cy5.5-NVs/FL-miR. (E) *Ex vivo* optical images of excised organs (liver, stomach, brain, lung, kidney, spleen, heart, and muscle) at 6 h after injection of Cy5.5-NVs/FL-miR. The intensity maps on the fluorescence images display normalized photon counts and (D) confocal microscopy images of tumor sections from mice treated with Cy5.5-NVs/FL-miR. Green, red, and blue represent FL from miR, Cy5.5 from NVs, and Hoechst 33342 from nucleus, respectively. Reproduced from Ref. [94] with permission of Elsevier.

(gold nanorods) can be used as direct NIR absorption imaging probes because their main absorption band is located in the NIR region due to the longitudinal surface plasmon.

Choi et al. noted that cRGD-conjugated gold nanorods showed excellent tumor targeting ability via NIR absorption imaging with no cytotoxicity. Additionally, the nanorods showed sufficient cellular uptake in a glioblastoma *in vivo* model, thus demonstrating their potential as $\alpha_v\beta_3$ integrin-targeted imaging probes [103, 104]. In particular, gold nanoparticles are useful for image-guided thermal therapy (also called hyperthermia or photothermal therapy) because they can absorb laser irradiation and convert the energy into a heat source via electron excitation and relaxation. Hyperthermia can induce apoptotic cell death in tumor tissues via heat generation, which provides a less invasive and localized therapy for cancer. As a result, it has been used to improve therapeutic efficacy and survival rates in combination with radiotherapy or chemotherapy for tumors. Choi et al. [105, 106] also prepared Cetuximab (CET)-conjugated gold nanorods and evaluated their hyperthermal properties under NIR irradiation (**Figure 9**). Gold nanorods have been frequently used to trigger hyperthermia in combination with an NIR laser, which is more effective for tissue penetration than are UV and visible light. After NIR laser irradiation, CET-PGNRs showed strong therapeutic efficacy in tumor-bearing mice, thus demonstrating the potential of CET-PGNRs for simultaneous

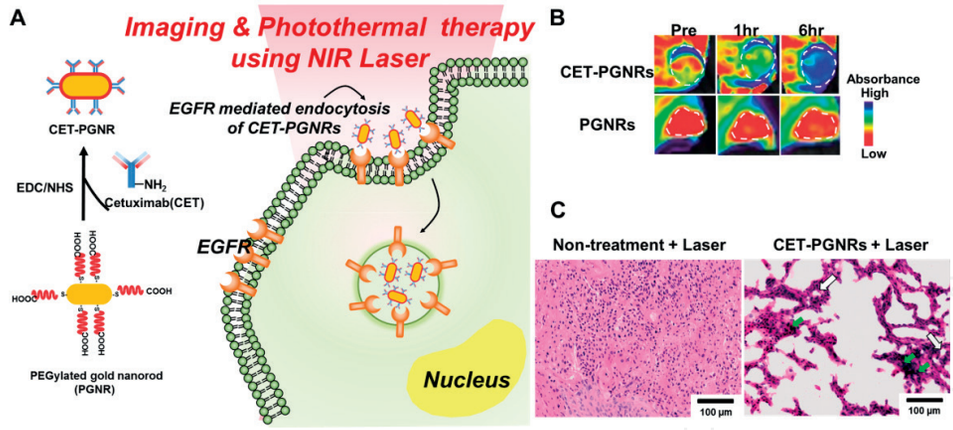

Figure 9. (A) Schematic illustration of CET-PGNRs as NIR absorption imaging and photothermal therapeutic agents for epithelial cancer. (B) Noninvasive NIR absorption *in vivo* images of tumor tissues for intravenous injected CET-PGNRs or PGNRs (control); white-dotted circles indicate the tumor regions. (C) Silver staining eosin. Tumor region was characterized by extensive pyknosis (green arrows) and cell vacuolization (white arrows) only in mice treated with CET-PGNRs after NIR laser irradiation. Reproduced from Ref. [12] with permission of ACS Publications.

absorption imaging and photothermal ablation of epithelial cancer cells with excellent targeting ability. Additionally, Choi et al. demonstrated highly sensitive terahertz (THz) molecular imaging using same probe (CET-PGNR) in both *in vitro* and *in vivo* models, indicating that its high thermal sensitivity can help extend photonic-based photothermal molecular imaging and be used for monitoring drug delivery processes and for early cancer diagnosis [105, 106]. Nam et al. developed "smart" gold nanoparticles that enable aggregation in mild acidic intracellular environments due to their hydrolysis-susceptible citraconic amide surface, which induces a shift in the absorption to longer wavelength, in the far-red and near-infrared (NIR) regions. This smart feature is useful for photothermal cancer therapy [107].

4.2. Optical imaging guided surgery

The primary goal of cancer surgery is to maximize the tumor excision and minimize the collateral damage. Molecular imaging techniques are required to achieve these goals, leading to "image-guided surgery" [108–117]. Especially, optical imaging is the most suitable for image-guided surgery (or targeted surgery) because fluorescence signals can provide real-time guidance to differentiate positive tumor margins and local malignant masses from normal tissues during surgery, thereby increasing the long-term patient survival. Near-infrared (NIR) imaging has particular potential to remove all neoplastic tissue at the surgical site because it is possible to obtain a low background signal and perform non-invasive real-time monitoring. Image-guided surgery is suitable for tumors that are difficult to differentiate from adjacent normal tissues (such as breast cancers), tumors that are next to complex structures with crucial physiological functions (such as brain tumors), or tumors that have high local recurrence or positive margin rates. Suitable probes for image-guide surgery must specifically detect and target cancerous tissues by showing maximum signal from the target and minimum signal from the background.

A natural fluorophore called protoporphyrin (PpIX) has been clinically used for image-guided surgical resection of brain tumors (glioblastomas), demonstrating that its fluorescence signals

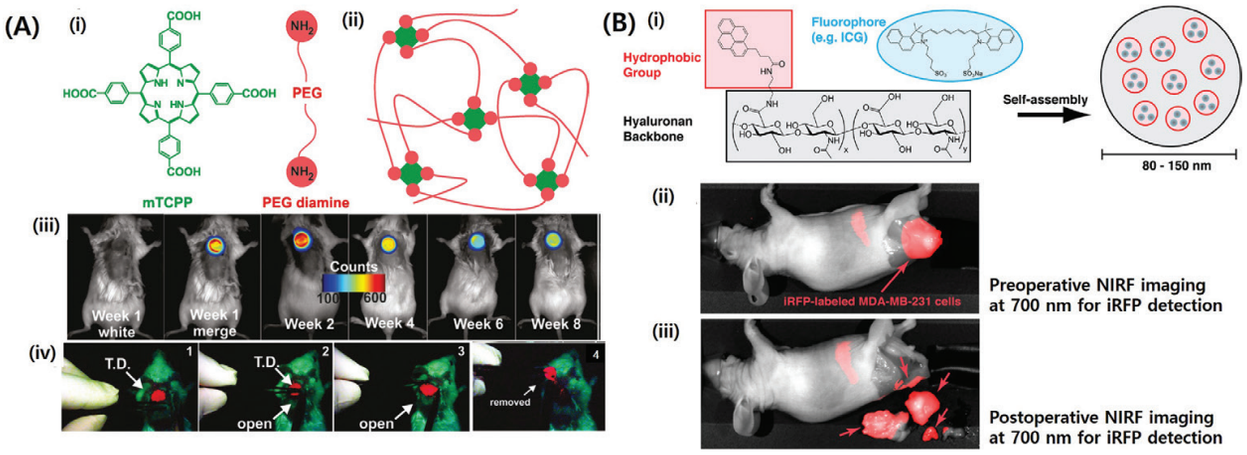

Figure 10. (A) Porphyrin-cross-linked hydrogels and noninvasive monitoring and image-guided surgical resection by using them. (i) Structures of mTCPP (green) and PEG diamine (red). (ii) Schematic of the hydrogel. (e), from left to right, (iii) fluorescence images of a mouse with the hydrogel implanted subcutaneously and monitored noninvasively. (iv) Screen captures from a fluorescence camera used to guide fluorescently the surgical removal of the hydrogel in real time. Fluorescence was readily apparent transdermally (T.D.) or through the open incision, as indicated. (B) Hydrophobic moieties conjugated to HLA drive self-assembly into nanoparticles that can entrap ICG. Indocyanine green-loaded nanoparticles for image-guided tumor surgery (i) hydrophobic moieties conjugated to HLA drive self-assembly into nanoparticles that can entrap ICG. (ii) Preoperative imaging and (iii) postoperative imaging of iRFP shows the location of MDA-MB-231 breast tumor xenograft. Red arrows indicated extracted tumors, where iRFP signal showed due to the presence of NanoICG. Reproduced from Refs. [116, 117] with permission of ACS Publications.

are highly specific to tumor cells. Lovell et al. [116] have developed hydrogels using cross-linked porphyrin co-monomers as strong optical tracers (**Figure 10(A)**). In *in vivo* studies, these could be used for the non-invasive fluorescence monitoring of subcutaneously implanted hydrogels over 2 months, without adverse effects or behavior. In addition, it was possible to non-invasively visualize where the gel was located and whether hydrogel degradation or photobleaching occurred. After surgical resection, while no residual fluorescence was detected in the mouse, hydrogel fluorescence was definitely recognized in the removed gel [116]. Hill et al. [117] demonstrated hyaluronic acid (HLA)-derived nanoparticles containing an indocyanine green (ICG) as near-infrared dye (NanoICG) for well delivery to tumors (**Figure 10(B)**). NanoICG exhibited quenched fluorescence and could be activated by disassembly in a mixed solvent (DMSO:H_2O = 50:50). Strong fluorescence enhancement of the NanoICG was observed in a breast tumor xenograft model. The NanoICG were more completely delivered to tumors compared to free ICG, with strong contrast enhancement in the tumor with a lower background signal in the surrounding tissue, thus demonstrating the potential of the NanoICG as a probe.

5. Conclusion

Optical imaging is a powerful tool that can provide the real-time and direct observation of specific molecular events, biological pathways, and disease processes. As described in this chapter, design strategies for imaging probes are important for accurate imaging to enable effective cancer management both *in vitro* and *in vivo*. Nanomaterial-based imaging probes can obtain

simultaneous imaging of multiple targets with high sensitivity, multimodal imaging, and imaging-guided therapy (theranostics) in combination with therapeutic agents. In particular, due to the advantages of optical imaging, the surgeon can simultaneously perform surgery while identifying where the cancer is located (imaging-guided surgery). These techniques will greatly contribute in reducing cancer recurrence and developing more effective cures.

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