

Chapter 8

Nanoparticle for Photoresponsive Minimal-Invasive Cancer Therapy



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Introduction

Cancer treatment is one of the most challenging problems confronting the world-wide healthcare system. The most common types are breast, lung, liver, stomach, and brain cancer, which are about ten million new cases every year. The cancer therapies used against this devastating disease are chemotherapeutic drugs, radiation, and surgical interventions. The choice of therapy depends on location, staging, and types of cancer (Sharker, 2019). Each of these therapies has some advantages and disadvantages because these cytotoxic treatments often kill healthy tissues and can cause resistance in cancer cells.

Another effective strategy that is currently gaining huge attention toward the researchers is the light-induced minimal-invasive cancer phototherapy, which includes photodynamic therapy (PDT) and photothermal therapy (PTT) (Gürbüz et al., 2020). In cancer phototherapy, the applied low energetic light has no interaction with the tissue area, and light can trigger externally from the body. The use of light to activate DDS for chemotherapy is yet another attempt to reduce the side effects and toxic effects of cancer chemotherapy. Moreover, combination treatments are a widely accepted strategy in cancer therapy, where surgical intervention, radiation, and chemotherapy are administered concurrently to cancer patients. It would therefore be desirable to develop photo-based therapies that may provide benefit from chemo- or radiotherapy with minimal adverse health effects (Huang & El-Sayed, 2011). The minimal-invasive therapy like chemotherapy, radiation, and phototherapy may gain popularity to cancer patients as they allow at least hospitalization, rehabilitation, and side effects.

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The use of light as a therapy dates back 3000 years. During that time, traditional Egyptians, Chinese, and Indians medicine used light to treat rickets, vitiligo, psoriasis, and other skin diseases. In modern medicine, Niels Ryberg Finsen received the Nobel Prize in 1903 for his treatments of cutaneous tuberculosis and smallpox pustules with ultraviolet (UV) and red light. This is the inauguration of a systematic study and understanding of the photochemical and photophysical processes of diseases and its treatment. As a result, the direct use of light has been used in vitamin-D deficiency, neonatal jaundice, manic depression, and other diseases (Tong & Kohane, 2012).

Light is a form of energy known as electromagnetic radiation (EMR). All types of light can travel at the same velocity with straight lines; however, they vary owing to the different sizes of wavelengths. For example, humans can visualize the spectral region of 400–600 nm of wavelength. Ultraviolet (UV) light has a shorter wavelength (200–400 nm), while infrared (IR) rays have a longer wavelength (600 nm–few μm size). Light consists of photons, and the wavelength of light is inversely proportional to energy ($E = h\nu$) (Tong & Kohane, 2012).

Based on the nature of medium in which it is propagating, light can be absorbed, transmitted, scattered, or reflected. The biological organic molecules, hemoglobin, and tissue heterogeneity have scattered and absorbed most UV and visible light, whereas the longer (650–900 nm) wavelength near-infrared (NIR) light can reach up to 10 cm depth. In this context, the maximum tissue-permeable NIR light and light-responsive NPs can be used for minimal-invasive optical imaging and phototherapy.

Minimal-Invasive Cancer Therapy

Moreover, the absorbed light can induce specific photochemical or photophysical reactions in the presence of light-responsive agents (Fig. 8.1). Those useful properties can be used for therapeutic or diagnostic purposes or both. The photochemical reaction included photo-cleavage or photo-switching, whereas the photophysical interaction included generation of cytotoxic singlet oxygen ($^1\text{O}_2$) or conversion of light into hyperthermia. Photoresponsive targeted cytotoxic $^1\text{O}_2$ therapy, known as photodynamic therapy (PDT), and photothermal heat-mediated therapy, known as photothermal therapy (PTT), are the main two branches of minimal-invasive cancer phototherapy (Gürbüz et al., 2020). At the same time, the emission of light at different wavelengths from light-responsive agents can induce bioimaging and diagnosis. Systemic study and understanding of photochemistry and nanotechnology in one platform has contributed to the clinical translation of promising NPs to address minimal-invasive PDT and PTT.

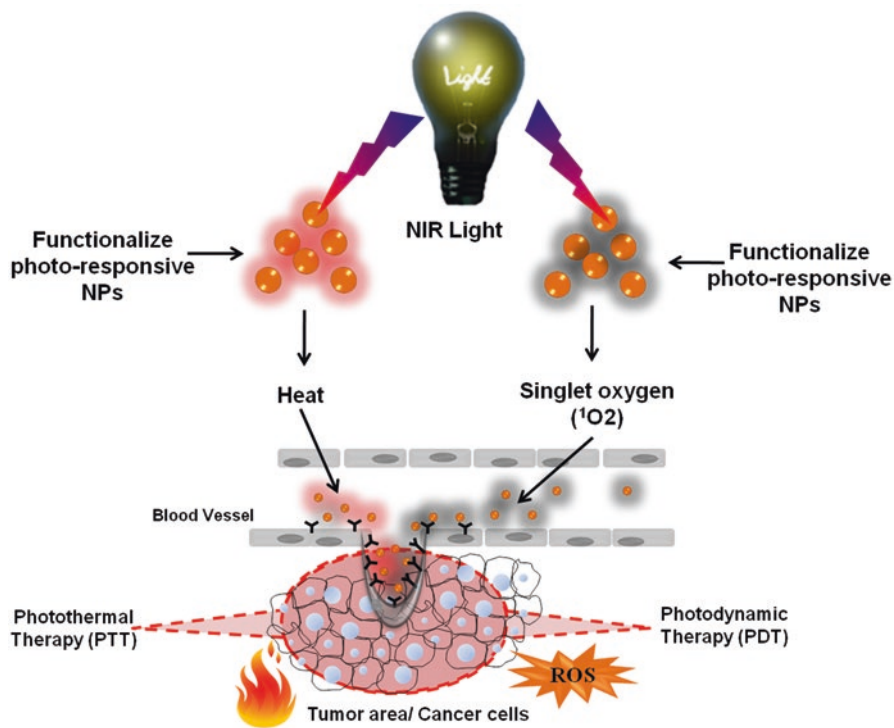


Fig. 8.1 Light-responsive nanoparticles (NPs) for the applications of PDT, PTT, and chemotherapy and theranostics

Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) needed photosensitizer (PS) agents, which are excited in the presence of molecular oxygen (O_2). The subsequent photochemical reactions have generated reactive oxygen species (ROS) and transform the molecular oxygen (O_2) to cytotoxic singlet oxygen 1O_2 species. The reactive and singlet oxygen species followed two pathways: direct necrosis and apoptosis and indirect microvascular damage and antitumor immune responses (Hou et al., 2018).

The first PDT-based clinical results were in a dermatological site for the treatment of skin cancer. The key challenges involved in this PDT are tissue thickness, dose of PS, and continuity of treatments. Moreover, traditional PS are facing difficulty in water solubility, stability, and untargeted activity with the diseased tissue. Additionally, typical PDT agents utilize short-wavelength (UV and visible) light for activation, which cannot penetrate deep inside the tissue. PS agents having targeted molecule-modified nanocarriers and upconversion (UC) nanomaterials which can convert long-wavelength excitation light to short-wavelength have the potential merits to improve curative effect and reduce side effects (Hou et al., 2018).

Moreover, several nanocarrier-based PDT agents also showed promising fluorescence imaging capability, which can empower imaging-guided therapy and diagnosis, following optimum cancer therapy. Currently, NIR-responsive organic fluorescence dye including ICG, IR825, and IR780 and inorganic and hybrid nanomaterials like gold nanoparticles, carbon nanotubes, and graphene oxide have performed improve and efficacious PDT (Kim et al., 2016a).

Photothermal Therapy (PTT)

Photothermal therapy (PTT) has utilized a photosensitizer (PS) which can convert light energy into heat to kill cancer cells (Hou et al., 2018). The tissue-penetrating near-infrared (NIR) light and tumor-targeted photothermal agents are the main two factors controlling the efficiency of PTT. The ligand-based active targeting and the nano-fabrication-based passive targeting strategy can be used to define the control delivery of PTT agents. Moreover, imaging modules, like fluorescence imaging-guided PTT, may have a precise tumor-killing effect. Typically, the temperature above 42 °C exerts antitumor effects by damaging the tumor cell membrane, destroying the cytoskeleton, and inhibiting DNA synthesis. The duration and extent of PTT can be optimized through controlling NIR laser power or the concentration of photothermal agents. However, increasing laser power is associated with biosafety issues, and photothermal agents might not provide complete biocompatibility (Hou et al., 2018).

Moreover, heat shock proteins (HSPs) may overexpress during PTT, which allow repair of protein damage and cell apoptosis. The tumor cells can get protection, and the resulting heat resistance slows down the effects of PTT. The use of antagonizing HSPs, such as HSP70 and HSP90, during treatment could overcome the failure of PTT. Additionally, PTT-based hyperthermia can activate immune response by secreting cytokines and upregulating the expression of HSPs. The innate immunity and the adaptive immune system activated by tumor-associated antigens and hyperthermia therapy can kill residual or metastatic tumors (Ali et al., 2016).

Combined Phototherapy and Chemotherapy

Chemotherapies are typically cytotoxic small molecular drugs that can kill fast proliferating cells. It is the first choice of cancer treatment, and chemotherapy can increase the life span of cancer patients when it is possible to cure cancer (Gürbüz et al., 2020). The main side effect of cytotoxic chemotherapeutic drugs is that it also affects normal healthy tissue like digestive tracts and the bone marrow. The therapeutic success depends on the extent of cytotoxicity between normal cells and cancer cells. Therefore, the choice of drug, the dosage, and their biodistribution determine the effectiveness of chemotherapy.

Moreover, because most chemotherapeutic drugs are poorly aqueous-soluble, they can only be administered one at a time, and their pharmacokinetic profiles allow them to be rapidly excreted before tumor accumulation. Those limitations can be overcome by developing nanocarrier systems for commonly used chemotherapeutic drugs including doxorubicin (DOX), docetaxel (DTX), cisplatin (CPT), and paclitaxel (PTX). In this context, the long blood circulation time of nanocarriers is required for sufficient accumulation at the tumor site. However, most nanocarriers are usually taken by the liver and spleen during blood circulation, and long-term deposition becomes a toxic effect for a particular organ. As a result, there are still challenges in preventing drug release during circulation and controlling supply at the tumor site (Gürbüz et al., 2020). Combinational therapies including radiotherapy with chemotherapy and PTT and PDT with chemotherapy can beat this challenge by corporately fighting cancer.

Photoresponsive Nanoparticles (NPs)

The incident light which is the basis of photoresponsive NPs can cause photon injury. It depends on power density, spot size, irradiation time, and wavelength of incident light. The most common photon injury is photothermal damage where rising temperature damages surrounding tissue through protein denaturation, detritions of molecular tertiary structure, and subsequent fluidization of membranes. Based on the power of photothermal heat, the cell may undergo apoptosis (55–58 °C), apoptosis and necrosis (60–68 °C), or direct cell death (72 °C or higher) (Tong & Kohane, 2012). The increased and controllable photothermal heat in a target tumor is used in PTT. The incident light can also interact with endogenous chromospheres, like heme proteins and flavoproteins for the generation of free radicals. The free radical is another form of photochemical damage in the living system. Typically, long-term exposure to high energetic (short-wavelength UV) light is responsible for such photochemical injury.

The American National Standards Institute (ANSI) recommended maximum permissible exposures (MPEs) for different energetic light. The MPEs depend on light duration, pulse of light, and wavelength of light (Tong & Kohane, 2012). For the 10 W cm⁻² (watt per square centimeter) power sources in a 700-nm continuous wave, it is no longer than 1 sec. In case of longer wavelengths, higher power fluxes are permissible. Typically, NIR-responsive NPs have been triggered by a 0.1–10 W cm⁻² power source with a continuous pulse laser in most cancer therapies.

Light-Responsive Plasmonic NPs for PDT, PTT, and Diagnosis

Photoresponsive NPs have been synthesized to perform cancer therapy and are classified into inorganic (metallic), organic (polymeric, liposome), and hybrid systems. The nanosized metallic nanoparticles are photoactive and have a distinct photophysical property. Metallic NPs possess free electrons which are oscillating on its surface. The incident light with similar frequency can interact with an oscillating electron, and the collective coherent oscillation of metal exhibits absorption of resonance light. However, based on size and shape, the metallic NPs can also scatter or couple incident light. The distinct photophysical properties of metallic NPs are known as localized surface plasmon resonance (LSPR) (Huang & El-Sayed, 2011).

Light absorption in metallic NPs is due to the loss of photon energy by inelastic (lost or increased) processes, whereas light scattering results in electronic oscillation of photon energy in NPs. Interestingly, the scattering phenomenon has contributed to the emission of photons with the same frequency as the incident light. The photophysical light absorption and scattering properties of metallic NPs can be explained by Mie theory. The presence of LSPR effect in most of the metallic NPs can increase both light absorption and scattering efficiencies. For example, inorganic gold NPs have 1000 times the absorption or scattering properties of any existing organic molecule. This makes them well-suited as photoresponsive agents (Fig. 8.2) (Huang & El-Sayed, 2011; Sharker et al., 2015a).

The unique LSPR of metallic NPs depends on the particle size, shape, structure, electron charge density, and the surrounding medium on the particle surface. For example, spherical gold (AuNPs), silver (AgNPs), and copper (CuNPs) nanoparticles have a strong light absorption band in visible areas, whereas other metallic NPs exhibit broad and weak absorption bands in the UV area. Furthermore, modified hollow structures or core-shell NPs can show a red shift (longer wavelength) when compared to unmodified NPs (Huang & El-Sayed, 2011). The shape of NPs, such as rods, triangles, or branch structure, can also red shift the wavelength, known as anisotropic effects.

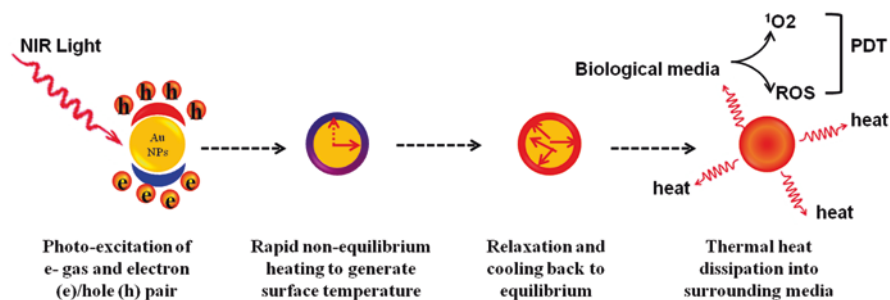


Fig. 8.2 Light-responsive plasmonic NPs and photochemical conversion for the applications of PDT, PTT, and chemotherapy and diagnosis

Among the different noble metallic NPs, the gold nanoparticle (AuNPs) has been explored more in cancer therapy. In cancer therapy, the LSPR frequency of AuNPs can be shifted to the NIR area by changing the structure and shape (Huang & El-Sayed, 2011). This is particularly important because the NIR light can penetrate significantly in biological tissue. For example, in core-shell NPs, the silica core at 100–200 nm and a shell of gold at 5–20 nm demonstrated coupling between the inner and outer shell surfaces for red-shifting of the absorption band. It has been found that decreasing thickness of the core-shell ratio can control predictable shift from visible to NIR absorption area. As a result, the absorption band changes from 700 nm to 1000 nm, owing to the decreasing shell thickness from 20 nm to 5 nm. The metallic LSPR frequency has decreased near-exponentially with the decreasing shell thickness-to-core radius ratio. The rational nano-chemical synthesis and nano-technology approach allow us to develop NPs according to our needs.

The surface of metallic NPs allows conversion of absorbed light energy into heat. This includes a series of photophysical processes where the absorbed light energy oscillates the surface electron of the metal. The simultaneous electron-electron and electron-phonon relaxation as a result of oscillating electrons has generated substantial hot electron temperature in this metallic lattice. At the end of this translation, the lattices cool again through phonon-phonon relaxation, but the heat is dissipated from the particles into the surrounding medium (Huang & El-Sayed, 2011). Such light-to-heat conversion and heat propagation can be strategically used to raise the local temperature of the local environment. For sufficient amounts, heat from these hot NPs can change the function of the cells and even destroy them. For example, in photothermal therapy (PTT), cancer cells can be hyperthermally destroyed by targeted delivery and irradiation of metallic NPs.

Moreover, photoactivated metallic NPs can generate cytotoxic singlet oxygen ($^1\text{O}_2$) that is used in another cancer therapy called photodynamic therapy (PDT). With respect to LSPR of metallic NPs, it is assumed that a low-energy state of some NPs can transfer energy from irradiated absorbed light to molecular oxygen (O_2). Though molecular oxygen is present in living cells, target delivery and generation of singlet oxygen can be used to destroy cancer cells.

In addition to photoresponse property, metallic NPs like AuNPs have the potential to be used in cancer diagnosis. It can be used as a contrast agent or luminescence NPs for bioimaging exploration. Furthermore, the photothermal property of AuNPs opens up the possibility of developing a heat-responsive drug delivery system (DDS). For example, temperature-responsive polymer-coated AuNPs and loaded drugs can release in response to rising heat. In liposome DDS, photothermal heat has shown microbubble generation, leading to breaking of the liposome and drug release (You et al., 2012). It can be accomplished upon light irradiation to trigger the release of drug for the maintenance of dose-response curve. Even though the biocompatibility and biodistribution of metallic NPs remain contradictory, light-trigger DDS is a promising branch for anticancer drug and gene delivery.

Light-Responsive Polymeric NPs for PDT, PTT, and Theranostics

Photoresponsive organic NPs have shown promising outcomes for cancer photo-therapy and diagnosis. Such organic NPs like liposome, polymeric micelles, polymersomes, and dendrimers possess favorable stability, biocompatibility, and biodegradability to satisfy clinical translation of diagnostic and therapeutic demand (Fig. 8.3). Moreover, organic NPs can be easily modified by a simple chemical route, which can load versatile drugs and deliver them to the targeted disease site without degradation.

The unique NIR-responsive organic NPs can efficiently harvest light for emission, allowing for versatile optical imaging while also acting as a PDT and PTT agent. Nonetheless, there are still some challenges, and further research is needed to address them for their future clinical translation. For example, some NPs are low photo-stable, do not intrinsically absorb light, and have a poor light-to-heat conversion efficiency (PTT), a low level of singlet oxygen generation (PDT), and clearance issues. To address this issue, novel conjugated polymer dyes, biodegradable biomaterials with attached cancer ligands, and antibodies must be developed for photoresponsive organic NPs. Moreover, the injection of a photo-cleavable or photo-switching moiety during NP synthesis can precisely overcome the above shortcoming. The photo-cleavable group can either disrupt or deform the NP structure where irradiate light can be absorbed the most to perform photoresponsive activity. Advance formulation strategy could control NP size less than 5 nm, which can solve clearance issues through urinary excretion. Thus, the interface of biology

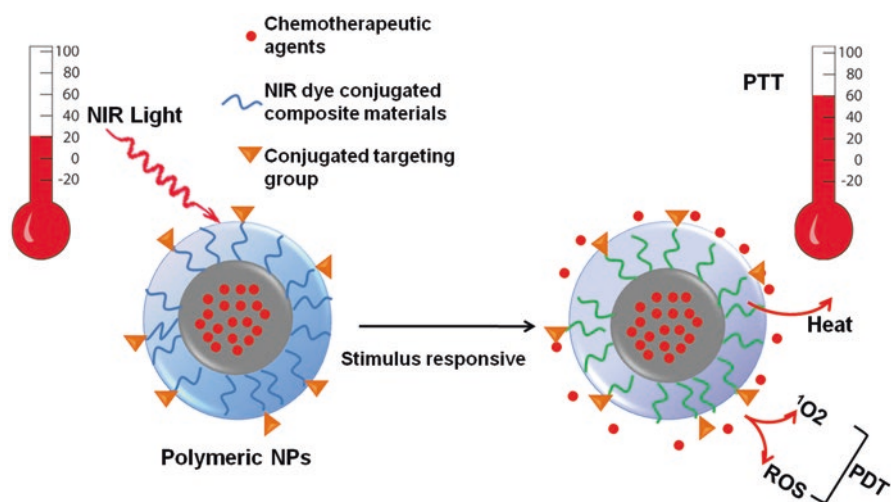


Fig. 8.3 Light-responsive polymeric NPs and functional modification for the application of PDT, PTT, and chemotherapy and theranostics

and chemistry in nanotechnology should be tailored for the application of NIR-responsive organic NPs clinically.

In photoresponsive NPs, the photochemistry and photoactivity of conjugated or loaded dye slightly differ when compared with free state. The free dye molecule absorbs light energy and releases fluorescence emission, whereas in nanosystems, the conversion of heat or singlet oxygen has been noticed in different organic photoresponsive NPs.

Previous studies showed that heat-sensitive liposomes loaded IR780 dye in its lipid layer and DOX loaded in the aqueous cavity can perform photoresponsive chemotherapy release. The mechanism was that the NIR laser excited IR780 to produce heat that will disrupt liposome structure, finally allowing DOX to be released from the liposome. In one example, organic NPs made by photocaging groups were shown to have an automatically degraded cleavage moiety, allowing loaded dyes to be released. Furthermore, organic NPs made with methoxy polyethylene glycol (mPEG) and poly(lactide-co-glycolide) (PLGA) conjugated to porphyrin have shown a micelle-like structure capable of loading both hydrophilic and hydrophobic drugs (Denkova et al., 2018). The release of those drugs could be controlled thermally by irradiation of NIR laser. The NIR light-irradiated organic liposome composed of pyropheophorbide has shown promising light to conversion efficiency for the use of PTT. Such systems can simultaneously deliver DOX during thermal therapy. The study and use of dual functional organic NPs have recently gain considerable interest, which might be due to PTT potentially improving the efficacy of chemotherapy.

Organic NPs photoactivated with photosensitizers can not only serve as phototherapeutic agents but also act as optical nanoagents for bioimaging. The NIR-absorbing organic nanoparticles or loaded MR (magnetic resonance), US (ultrasound), and CT (computed tomography) contrast within organic NPs endow them with single-modal or multimodal imaging-guided cancer therapy. Previous biological activity studies performed on photosensitizer organic NPs revealed that they should be water-soluble and tumor-targetable, have a high yield of heat or singlet oxygen generation, and be rapidly eliminated from healthy tissue.

Light-Responsive CDs for PDT, PTT, and Theranostics

Carbon dots (CDs) offer the development of theranostic (therapeutic and diagnostic) nanoparticles for combined cancer imaging and therapy. The fascinating photoluminescence (PL) property of CDs can be used in different biomedical fields accurately, like cancer diagnosis and therapy. Typically, the CDs show a full absorption spectrum in the ultraviolet (UV) region, owing to the extensive π -conjugated electrons in an sp^2 atomic framework. It attributed π - π^* transition for aromatic C=C bonds and n - π^* transition for the C=O bonds or other connected groups. Additionally, the CDs with different size, composition, structure, or surface passivation effect can change its light absorption spectrum (Kim et al., 2016a; Gupta et al., 2014).

However, the emission spectrum of CDs shows excitation-dependent behavior ranging from UV to visible or near-infrared (NIR) region. Therefore, it is highly promising for multicolor bioimaging applications. Although the mechanism of PL emission is still a controversial issue of CDs, it is an important tool for biomedical use. For this, there are two proposed mechanisms: the quantum confinement effect (QCE) mechanism based on the band gap of the conjugated π -electron and the edge effect mechanism based on the surface defect states of both sp^3 - and sp^2 -hybridized carbons. This result has increased the localization of electrons on CDs and contributes to multicolor fluorescence emissions. Furthermore, the inherent photostability and introduction of surface passivation properties could amplify the fluorescent properties and empower the biological application in different ways. In the case of surface passivation (functionalization), the increased densities of the π -electron have facilitated the radiative combination and the quantum confinement of electron-hole (e/h) pair that improves fluorescent properties of raw CDs (Sharker et al., 2015b) (Fig. 8.4).

CDs or FCNs (fluorescent carbon nanoparticles) are considered an excellent luminescence probe for bioimaging due to their unique optical properties, size tuning capacity, surface functionalization capacity, and less photo-blinking and photo-bleaching characteristics (Sharker et al., 2015b). Though the surface functionalization of CDs is a complicated engineering method, the resultant fabricated and functionalized CDs are capable of exhibiting multiple functions. They can work as a remarkable drug carrier system and a gene delivering aid. Still, they can also be modified as an excellent phototherapeutic agent and sensor molecule for various therapeutic and diagnostic purposes, possibly due to their maximum drug-loading capacity (Choi et al., 2014). Numerous *in vitro* and *in vivo* studies have shown low or non-toxic nature of CDs compared to other fluorescent nanomaterials. Moreover, there is the ease of administration of CDs via different routes, such as oral, nasal, and parenteral, which make them better and more convenient forms of drug delivery systems to deliver therapeutic substances.

The ability to generate detectable acoustic waves in response to excitation waves is another attractive property of CDs, which can work as contrast agents in

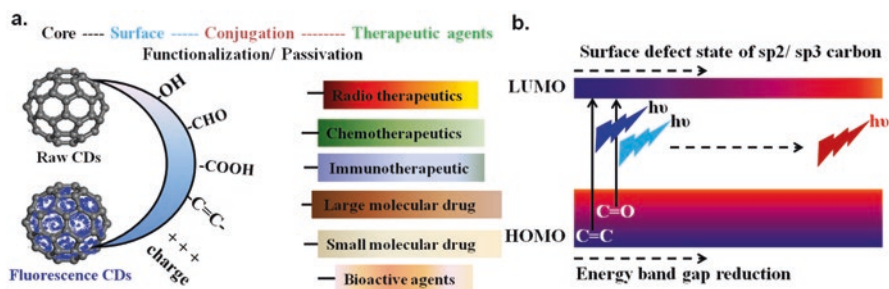


Fig. 8.4 (a) The photoresponsive carbon dot (CDs) NPs and the potential applications for PDT, PTT, and chemotherapy and diagnosis, (b) the light-responsive fluorescence and energy conversion process of CDs

photoacoustic imaging. An essential feature of photoacoustic imaging is that it offers an excellent spatial resolution to monitor the smallest areas, like axillary lymph nodes in breast cancer. Moreover, light-triggered photosensitizing properties of CDs alone or, in combination with photosensitizing agents, can generate reactive oxygen species (ROS) in tumor cells. This is another branch of cancer therapy, commonly known as near-infrared (NIR) light-irradiated photodynamic therapy (PDT). For example, PEG-functionalized CDs with photosensitizer chlorin (Ce6), protoporphyrin, or zinc phthalocyanine (ZnPc) were generated ROS under the excitation of CDs for targeted PDT (Choi et al., 2014).

Like PDT, the NIR-responsive photothermal therapies (PTT) can hyperthermally kill the targeted cancer cells. Different carbon-based NPs have this ability to absorb NIR light in the electromagnetic spectrum and consequently convert into reasonable heat to thermally destroy the malignant cells. For example, the carbonized polydopamine (pDa) have performed NIR-responsive photothermal conversion and multi-color fluorescence emission in different excitation wavelengths (Kim et al., 2016a). Moreover, CD-based hybrid systems can simultaneously perform PDT, PTT, and pH or NIR-responsive drug release. Such a multifunctional smart delivery system enables synergistic cancer therapy. For example, PEG chitosan-integrated CD nanogels have shown pH and NIR light dual-responsive drug release and PTT against tumor cells. In another attempt, carbonized fluorescence hyaluronic acid (HA-FCN)-conjugated boronic acid (BA) with β -cyclodextrin showed multi-responsive paclitaxel (PTX) DDS (Sharker et al., 2015c). This kind of DDS exploits acidic pH-dependent and remote external NIR-responsive on-demand cooperative controlling strategy. Such development of cooperative stimulus-responsive DDS having bioimaging potentiality is a promising method for chemotherapeutic release that can be adjusted according to physiological needs (Sharker et al., 2015b).

Light-Responsive CNTs for PDT, PTT, and Theranostics

The carbon nanotubes (CNTs) are one-dimensional (1D) needle-like structures which have generated significant interest in cancer therapy and diagnosis. Structurally, the CNTs are sp²-hybridized cylindrical tube-like shape carbon-based nanomaterials. The CNTs are prepared by rolling single- or multi-layered sp² carbon, known as single-walled carbon nanotubes (SWNTs) and multi-walled carbon nanotubes (MWNTs) (Liang & Han, 2006). The unique CNTs belong to a vast surface area that can load small molecular as well as large molecular drugs and diagnostic probes.

The CNTs are soluble in a wide range of solvents and can be covalently functionalized on their side walls and the edge of tubes. The functionalization of CNTs is a first step to load the therapeutic agents. Moreover, conjugation of a diagnostic probe would provide added advantages for bioimaging, detection, and monitoring of the treatment process. The potential applications of CNTs can lead to the development of several new drug delivery systems that are still poorly explored.

The CNTs, specifically SWNTs, have intense NIR absorption bands due to the presence of intact sp²-hybridized carbon sheets resembling graphene. It has been found that the NIR light absorption band has decreased with an increased level of chemical conjugation. However, the chemical functionalization offers greater water solubility and biocompatibility. The mechanism behind the NIR responsiveness is that the energy levels of one-dimensional (1D) SWNTs have split due to quantum confinement effects. The 1 eV (electron volt) energy band gaps between the SWNTs allowed exciton wavelength-dependent fluorescence emission in the NIR area (Barone et al., 2005). The characteristic Stokes shift (energy band gaps) in this NIR area provided lower autofluorescence of biological tissues during bioimaging and diagnosis.

The incident light absorbed by NIR-responsive SWNTs can act as a photochemical catalyst in surrounding molecules. The photochemical reactions organized by SWNTs with molecular oxygen (O₂) are able to generate cytotoxic singlet oxygen (¹O₂). The photodynamic conversion of cytotoxic ¹O₂ can play a key role in cancer PDT. Although several photoresponsive NPs have already shown promising PDT, the SWNTs can be an interesting one due to NIR responses. For example, the non-covalent conjugation of SWCNTs with pyrenyl-functionalized distyryl-BODIPY has shown PDT agent in response to 660 nm light. In another study, photosensitizer 5-aminolevulinic acid-loaded polyamidoamine dendrimer-modified MWCNTs exhibited photodynamic destruction of tumor when they were excited to 632 nm light. Furthermore, the zinc monocarboxyphenoxy phthalocyanine (ZnMCPPc) with spermine- and uridine-loaded SWCNTs have shown high level of triplet and ¹O₂ yield for the efficient PDT against melanoma A375 cells (Gupta et al., 2019).

Concurrent diagnosis and therapy is the key feature of CNTs in cancer theragnostics. The CNTs allowed broad electromagnetic absorbance spectrum in the NIR windows that can be a unique feature for the development of next-generation photothermal agents (Singh & Torti, 2013). This is because the NIR-responsive CNTs can efficiently convert the absorbed light into heat for the photothermal ablation of tumors. The absorbed NIR light allows CNTs to migrate excited states, and when it does, it releases absorbed energy in the form of vibrational energy, which is converted into heat energy to exhibit photothermal therapy (PTT). Moreover, it has been observed that the broad absorption window of CNTs is more advantageous than that of plasmonic metallic NPs, whose absorption band changes with size and shape of particles.

The photothermal studies of CNTs are well-known established methods in cancer therapy. However, the exciting result has been found in NIR-induced treatment of vascular inflammation, remote control gene expression, and implantable bioelectronic devices operated by laser irradiation from outside the body (Singh & Torti, 2013). Moreover, combining PTT and PDT can be a more efficient cancer treatment than only PDT or PTT. For example, Ru(II) complex SWCNTs (Ru-SWCNTs) produce ¹O₂ through the photothermal effect of this complex, which exhibits enhanced anticancer efficacy. It is not surprising that new engineering strategies and unique functionalization schemes of CNTs have tremendous potential for human biological use.

Light-Responsive Graphene Oxides for PDT, PTT, and Theranostics

Graphene and its derivative graphene oxide (GO) have shown the most promising nanomaterials for cancer diagnosis and therapy. Structurally, graphene is two-dimensional (2D) and sp²-hybridized, and GO consists of both sp²- and sp³-hybridized planar carbon sheets. The planar carbon sheets bonded together to form a π -conjugated hexagonal pattern like a honeycomb. The basal plane of GO consists of a network of sp²- and sp³-hybridized carbons bearing hydroxyl (-OH) and epoxide (-O-) groups, whereas the edges are furnished by carboxyl (-COOH) and carbonyl (-CO-) functional groups (Lin et al., 2014; Kim et al., 2015).

The source of carbon-based GO is mainly graphene, which is available everywhere and can be prepared at a low cost. An essential feature of GO on its basal plane is pi-pi stacking/interaction, which can attach various molecules to its surface. Additionally, the carboxyl (-COOH), carbonyl (-CO-), and hydroxyl (-OH) of graphene oxide allow the conjugation of different therapeutic agents. The attached and conjugated GO nanocomplexes have the potential to improve the aqueous solubility of different anticancer therapies, a major problem facing most chemotherapeutic agents. The experimental results GO nanocomplexes promise to deliver a broad range of therapeutic agents in upcoming advanced drug delivery systems. In recent years, the analyses of GO nanocomplexes have led us to believe that it has the potential to solve cancer diagnosis and therapy at an early stage (Kim et al., 2015).

The GO can conjugate with organic photosensitizer through π - π stacking, hydrophobic interactions, and electrostatic interaction (Karimi et al., 2017; Sharker et al., 2016). The versatile interaction allows for increased loading efficiency and highly efficient PDT. Moreover, PDT can achieve the cancer target with the simultaneous conjugation of a targeting ligand. The photodynamic activities are caused by lipid peroxidation, depolarization of mitochondrial, increased caspase-3 activity, and finally apoptosis and death of target cancer cells.

The novel features of photosensitizer-loaded GO make them well-suited for cancer therapy. For example, chlorine e6 (Ce6), zinc phthalocyanine (ZnPc), and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide- α (HPPH) molecules loaded with PEGylated GO have shown high-rated singlet oxygen production ability sufficient for PDT (Kim et al., 2016b). Even though their fluorescence emission intensity has decreased due to the quenching properties of graphene oxide, their cellular uptake and permeability are very promising.

The GO sheets have broad UV to NIR absorption windows, which can be a potential candidate for hyperthermia cancer therapy (PTT). The presence of characteristic band gaps and edges/defects of GO has contributed reasonable photoluminescent properties and produces intensive heat at the time of laser irradiation. In PTT, the heat production efficiency depends on light absorbance ability. The light absorption efficiency of GO can be increased significantly when it is reduced. The reduced graphene oxide (rGO) can be developed through chemical and physical approaches including heat and light exposure. Moreover, polyethylene glycol (PEG)

and hyaluronic acid (HA)-modified biocompatible GO and fluorescent dyes such as Cy7, Hilyte647, or rhodamine B-loaded GO have shown bioimaging-guided PTT when they were applied into xenograft mice (Kim et al., 2016b).

GO can attach hydrophobic aromatic compounds like anticancer drugs by π - π stacking and hydrophobic interaction. The strategic design of GO-drug complex with a targeting agent can serve as a controlled drug release system. The nanosized GO carrier system belongs to a vast surface area and showed better accumulation in tumor microenvironments (Sharker et al., 2015d). Moreover, PDT and PTT can be anchored with this carrier system to achieve multimodal cancer therapy.

Previous studies showed that doxorubicin (DOX) can be released from the PEG-GO-DOX complex in response to glutathione (GSH) and NIR hyperthermia treatment. The NIR-induced photothermal heat has disrupted the endosome, which allows GO-DOX to escape into the cytoplasmic matrix. In other studies, the PEGylated GO with branched polyethyleneimine (BPEI) has performed combined DOX delivery and PTT. The interesting layer-by-layer methods were used for GO-poly (allylamine-hydrochloride)(PAH) nanocomplexes and pH-responsive drug delivery and PTT simultaneously. The photothermal chemotherapy may reduce chemotherapy resistance, which has prompted extensive study in this area. For example, the protein-functionalized reduced graphene oxide (rGO) nanosheet showed stimuli-responsive controlled DDS. The multifunctional GO-IONP-PEG-DOX complex was developed by superparamagnetic graphene oxide-iron oxide with loaded DOX, which showed NIR-responsive PTT, magnetically targeted DOX delivery, and magnetic resonance (MR) imaging of tumor (Kim et al., 2016b).

Conclusions

A collective effort from nanotechnology has required the development of cancer phototherapeutics to overcome the hurdle of translating photoresponsive NPs. The preliminary works of photoresponsive NPs are very promising because of small sizes, functionalization potentiality, and the ability to introduce multiple therapeutic agents on its surface. Moreover, the photoluminescence properties of photoresponsive NPs play an additional advantage for the bioimaging and diagnosis of tumors. The combined therapeutic with diagnostic functionality is known as theranostics, which holds the main potential of photoresponsive NPs to address the challenges of cancer therapy. It can be a paradigm shift in the way that we traditionally treat cancer. In photoresponsive NPs, cancer therapeutic is still in the midst of development; however, it has the technical capability to develop a brand-new DDS that can bring new hope for diagnosing, treating, and preventing cancer in the near future.

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