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Nanotechnology-based photoimmunological therapies for cancer

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Abstract

Phototherapy is a non-invasive or minimally invasive therapeutic strategy. Immunotherapy uses different immunological approaches, such as antibodies, vaccines, immunoadjuvants, and cytokines to stimulate the host immune system to fight against diseases. In cancer treatment, phototherapy not only destroys tumor cells, but also induces immunogenic tumor cell death to initiate a systemic anti-tumor immune response. When combined with immunotherapy, the effectiveness of phototherapy can be enhanced. Because of their special physical, chemical, and sometimes immunological properties, nanomaterials have also been used to enhance phototherapy. In this article, we review the recent progress in nanotechnology-based phototherapy, including nano-photothermal therapy, nano-photochemical therapy, and nano-photoimmunological therapy in cancer treatment. Specifically, we focus on the immunological responses induced by nano-phototherapies.

Keywords

photothermal therapy; photodynamic therapy; photoimmunotherapy; nanotechnology; cancer treatment

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1. Background

Cancer is a serious public health problem in the world and its incidence has continued to rise throughout the last few decades. The American Cancer Society estimates that there were over 1.6 million new cases of cancer and over 600,000 cancer deaths in the United States during 2017 [1]. Cancer metastasis is the leading cause of treatment failure and cancer-related deaths. Unfortunately, many patients already have either detectable metastases or undetectable micrometastases throughout their body by the time they are diagnosed with cancer, and surgical resection is not a viable option [2]. In the past several decades, a number of new therapeutic strategies have been developed to combat metastatic cancers including targeted therapy, hormonal therapy, and immunotherapy, all of which have been effective in treating certain types of cancer. However, long-term survival rates are still not satisfactory [3].

The human immune system contains powerful mechanisms to destroy foreign substances within the body [4]. Immunotherapy is a cancer treatment modality designed to either instigate or enhance an antitumor response from the host immune system [5–6]. In recent years, more immunotherapy approaches have been developed, including cytokine therapy [7], tumor vaccination [8,9], immune-activating antibodies [10], and other methods. However, many cancers are inherently immunosuppressive, and are difficult to controlwith current immunotherapy [11–13].

Metastases form from primary cancer tumors, meaning both metastatic and primary cancer cells share common molecular markers on their surface. The ideal cancer treatment strategy not only destroys the primary tumors but also triggers the body’s immune system to destroy metastases and residual primary tumor cells. With this goal in mind, several advanced cancer therapies have been developed that combine topical therapies with immunotherapy [14–16]. These advanced cancer therapies maintain many of the advantages of immunological approaches, such a systemic response and a long-term antitumor immunity, while increasing the efficacy and response rates of the treatment [17].

Phototherapy, particularly using lasers to deliver energy to the target tissue, has been proven to be an effective therapy for treating primary tumors. Nanotechnology is widely used to enhance phototherapy, as nanomaterials can be designed to act as either a photosensitizer or a photothermal transducer. Several nanomaterials with these capabilities have become popular, such as gold nanoparticles like gold nanorods (GNRs), [21] gold nanocages [22], carbon nanoparticles such as single-walled carbon nanotubes (SWNTs) [23], sulfide nanomaterials such as copper sulfide (CuS) [24], and black phosphorus [25]. Phototherapy-enhancing nanomaterials can be further modified with immunostimulants or other immunological drugs to induce systemic anti-tumor immune responses. These nano-photoimmunological therapies (NPIT) have shown prospect for broad clinical application, particularly for treating metastatic cancers [18–20].

The toxicity of nanomaterials is a concern for their biomedical application. Many studies have demonstrated that SWNTs are potentially hazardous. The high-aspect ratio and biopersistence of SWNTs has led to toxicity akin to asbestos when inhaled [26]. However,

for most cancer therapeutics using nanoparticles, SWNTS are administered *in situ*. Such use of SWNTs leads to cytotoxicity and genotoxicity from chemical interactions with the graphene surface, electrically-charged imperfections in the graphene structure, and metal catalyst impurities that remain from the synthesis process [27]. When large doses of SWNTs enter the bloodstream, they initially deposit in the brain and lung tissue. SWNTs eventually clear to the liver where they affect the organ biochemistry long-term [28]. However, the biologically-harmful effects of pristine SWNTs can be ameliorated by appropriate functionalization of the SWNT surface [29–31]. Still, the potential toxicity of SWNTs remain a considerable barrier to their future clinical applications.

Many other nanoparticles have fewer concerns regarding potential toxicity. Gold nanoparticles are considered fundamentally inert, especially when functionalized, and the harmful surfactants used during manufacture, such as CTAB, are removed [32–33]. As a result, gold-based nanostructures could see imminent medical applications. Similarly, copper sulfide nanoparticles are biodegradable, cleared through hepatobiliary and renal excretion, and generally considered nontoxic [34–35]. Black phosphorus nanoparticles show acute cytotoxicity leading to local inflammation, but no long-term pathological changes in organs such as the liver and kidneys have been observed [36]. However, toxicological understanding of copper sulfide and black phosphorus nanoparticles is still preliminary, and more work must be completed before an accurate toxicology can be ascertained.

2. Nano-phototherapies

At the end of the nineteenth century, Niels Finsen began to treat diseases using phototherapeutic approaches [37]. He utilized red light to treat the formation and discharge of smallpox plica, marking the beginning of modern phototherapy. Currently, phototherapy is used to treat skin diseases, cancer, and many other ailments. The isolation of porphyrins and their interactions with light have led to a form of cancer therapy which is based on inducing oxidative stress in the tumor cells. Thus, modern cancer phototherapies can be categorized as either inducing oxidative stress or thermal stress called photodynamic therapy (PDT) or photothermal therapy (PTT), respectively [38–40].

2.1 Nano-photothermal therapy

PTT is a therapeutic strategy used to treat localized cancers. PTT is a minimally-invasive treatment that destroys tumor cells by generating heat through light absorption in the tissues [41]. PTT has been used in the clinical treatment of breast cancer, liver cancer, melanoma, and many other malignant tumors [42–44].

The use of a noninvasive light source implies that non-tumor tissues in the light path will also absorb energy from the laser, resulting in healthy tissue damage and reduced energy reaching the target tumor. To circumvent this problem, photothermal absorbers are used to enhance the light absorption efficiency within the target tumor tissue.

Obtaining light absorbers with high photothermal conversion efficiency has become an important task to improve PTT. For instance, the optical dye indocyanine green (ICG) has an absorption peak around 800 nm. ICG is useful for biological applications, as mammalian

tissue is relatively transparent to 800-nm laser light. Administering ICG into the target tissue prior to laser irradiation produces a specific absorption effect below the tissue surface, allowing for selective photothermal destruction [45–47] (Figure 1).

New photothermal transducers with different light-absorbing properties have been developed to increase the selectivity of laser treatments [48–50]. The development of new photothermal transducers must be non-toxic and ideally target the tumor on a molecular or physical basis. Additionally, mammalian tissues are relatively transparent to near-infrared (NIR) light, so photothermal transducers should absorb light in the NIR range to take advantage of this tissue penetration window when treating deeper tumors [51].

Ratto et al. reported that colloidal gold nanorods (GNRs) had the maximum absorption of 700-nm to 1300-nm light, and the laser energy was converted into heat by means of surface plasmon resonance [41]. As a photothermal converter, GNRs can drastically increase the tissue temperature and ablate local tumors effectively. Surface modification of GNRs can also be achieved relatively easily through attachment by a thiol group or other techniques [53–55].

Compared with GNRs, SWNTs have a wider range of electromagnetic absorption spectra, which enables more flexible selection of excitation wavelength [56]. The photothermal conversion efficiency of SWNTs is superior to that of GNRs, in that SWNTs can generate the same amount of therapeutic heat with less irradiation dose [57]. SWNTs can effectively treat tumors in conjunction with PTT. In the study by Moon et al., SWNTs injected into tumors followed by PTT treatment, completely destroyed the tumors with no recurrences, while the surrounding healthy tissue remained intact [58].

In addition to nanorods and nanotubes, ultra-small black phosphorus quantum dots (BPQD) have been used to treat tumors. Sun and his collaborators used ultrasound to obtain ultra-small BPQD with 28.4% photothermal conversion efficiency at 808 nm [25]. By conjugating polyethylene glycol (PEG) to the surface of the BPQDs, they are no longer cytotoxic to different types of cells. With NIR laser irradiation, the BPQDs can induce a strong photothermal effect, resulting in significant cancer cell killing.

With the use of these nanomaterials, researchers have made significant improvements in the efficacy of PTT. However, the thermal effects of PTT can increase the expression of heat shock proteins within cancer cells, allowing them to tolerate high temperatures and reducing the therapeutic effects[59]. Therefore, obtaining high-efficiency, low side-effect selective PPT using photothermal conversion materials may depend on the further development of appropriate nanomaterials.

2.2 Nano-photochemical therapy

Different from PTT, the main working principle of photochemical therapy is to use low-energy light in conjunction with a photosensitizer to generate reactive oxygen species (ROS) in tumor tissues through photochemical reactions. PDT is an example of photochemical therapy (Figure 2). PDT is approved by the U.S. Food and Drug Administration and has been used in the clinical management of many malignant tumors such as non-small cell lung

cancer, esophageal cancer, melanoma, and bladder cancer [60–64]. PDT enables therapeutic targeting of localized tumors, thus protecting normal tissues. PDT is has low tissue penetrance, because it utilizes light wavelength below 800-nm, and is commonly used to treat skin tumors or superficial malignancies under endoscopic guidance [65].

The oxygen content in the tumor tissue, light energy, and the efficiency of the photosensitizer are all important limiting factors for the killing effect of PDT. ROS cytotoxicity leads to both apoptosis and necrosis so as to achieve tumor cell destruction [66–67]. The lifespan of the ROS is short, approximately only 0.03–0.18 microseconds in tissues; therefore, the diffusion range of the ROS is limited [68–69]. The targeting effect from a photosensitizer is also of great importance in tumor treatments [70–71]. PDT-induced ROS must be generated in an aerobic environment, so the applicability of the treatment is subject to certain restrictions. Some tumors in a hypoxic environment could have only limited therapeutic effect. However, photosensitizers, such as semiconductor quantum dots and TiO_2, can generate significant amounts of ROS even under hypoxic conditions with PDT [72–73]. Idris et al. reported a method of encapsulating merocyanine 540 (MC540), zinc phthalocyanine (ZnPc), and an up-converting nanoparticle for use as PDT photosensitizers [76]. When using NIR laser irradiation, this novel combination greatly increases the production of ROS compared to the single up-conversion of nanoparticles by MC540 or ZnPc alone, resulting in a better tumor killing effect.

Chen et al. reported the use of $SrAl_2O_4$: Eu^{2+} (SAO) as a photosensitizer in combination with X-ray for PDT [77]. Unlike visible light and NIR light, X-ray photons have greater penetration in body tissues. If the PDT effect is activated by X-ray, it is feasible to treat tumors in any part of the body. The nanoparticle used by the researchers was composed of a core made of SAO with a silica coating loaded with the photosensitizer MC540. SAO converts X-ray photons to visible-light photons which is the phenomenon known as X-ray excitation of optical luminescence (XEOL). Matching the excitation wavelength of MC540, XEOL activates MC540 to generate cytotoxic ROS [78].

To overcome the limits on penetration depth from external light sources, others designed nanomaterials that generate chemiluminescent reactions. Yuan et al. used the reaction of luminol, hydrogen peroxide, and horseradish peroxidase (HRP) to generate light photons and cationic oligomeric p-phenylene vinylene (OPV) as a photosensitizer [79]. The photon generated from the oxidation of luminol is absorbed by an OPV molecule, which produces ROS through interactions with nearby oxygen molecules. This design has the advantage of producing light continuously, which extends the duration of photochemical therapy to get better clinical results.

With the combination of nanotechnology, PDT has made great progress in extending the depth and prolonging the duration of treatment for more effective responses.

2.3 Nano-photochemical therapy combined with photothermal therapy

In addition to the nanomaterials used for PDT or PTT alone, a number of new synthetic nanomaterials can be used both for PDT as photosensitizers and for PTT as photothermal

converters [80]. With such a combination, ROS can be generated while the temperature in the tumor is increased simultaneously to synergistically kill cancer cells.

The photosensitizer Chlorin e6 (Ce6) and GNRs can be connected via an aptamer switch probe (ASP). With light irradiation, the photosensitizer generates ROS. Simultaneously, the GNRs generate heat to destroy the tumor cells [81]. Similarly, GNRs combined with rose bengal (RB) molecules generated ROS and heat with simultaneous irradiation of 532-nm green light and 810-nm light [82]. The ROS produced by green light and hyperthermia generated by NIR light constituted two distinct mechanisms of cancer cell death. In addition, RB-GNRs also show improved photodynamic efficacy by enhancing the uptake of RB by cancer cells. Gao et al. implanted photosensitizers in mixed lipid-coated gold nanoparticles to construct a new bioconjugate nanostructure [83]. This nanostructure is internalized by cancer cells, and the anti-cancer effects of PTT and PDT are significantly enhanced concurrently under two-photon irradiation. Compared with being used for PTT or PDT alone, these multimodal nanomaterials can lead to synergistic therapies to improve tumor killing efficiency.

3. Photoimmunological therapy

Phototherapy-induced apoptosis or necrosis of cells can be an excellent source of tumor antigens. In combination with phototherapy, immunotherapy fully utilizes the tumor antigens to trigger an anti-tumor immune response. As a result, photoimmunological therapy is capable of treating metastatic cancers. This treatment strategy can be realized in a number of approaches (Figure 3).

3.1 Immune response induced by phototherapy

Phototherapy produces targeted tissue destruction. Even without the complete destruction of the target tumors, phototherapy can cause tumor cells to swell and lyse, resulting in the release of tumor antigens [84–85]. These antigens include tumor-associated antigens, heat shock proteins (HSPs), and other danger associated molecular patterns (DAMPs) [86–87]. Antigen-presenting cells (APCs), particularly dendritic cells (DCs), can capture these antigens and migrate to the lymph nodes, where they present the antigens to T cells inducing an anti-tumor immune response [88–89]. Phototherapy can enhance the expression of HSPs in tumor cells, especially on the surface of apoptotic cells. In particular, HSP70 acts as an endogenous danger signal to the immune system [90]. Innate and adaptive immune cells can recognize HSP70 expressed on the surface of tumors, and initiate its destruction (PMID: 17551095, 17911639). Additionally, extracellular HSP70 can stimulate the maturation of APCs (PMID:11465118, 25681671) and form HSP-peptide complexes promoting cross-presentation of HSP-conjugated peptide antigens in DCs. As a result, the mature DCs trigger the activation and differentiation of antigen-specific helper and cytotoxic T cells [91–92]. The role of HSPs in immune stimulation, at least in part, can explain the molecular mechanisms by which the host receiving phototherapy generates an effective immune response [93]. Phototherapy can also trigger the release of other DAMPsthrough tumor necrosis. DAMPs consist of proteins, RNA, and DNA that are normally found within cells. However, when released by dying cells, DAMPs activate APCs similarly to pattern

associated molecular patterns (PAMPs) expressed by pathogens. Thus DAMPs released in response to tumor necrosis are associated with enhanced immune responses [94].

Phototherapy can release tumor antigens through localized selective photothermal or photochemical effects to form an *in situ* cancer vaccine via activation of the host immune system [95]. However, the tumor fragments produced by phototherapy may not be sufficient to induce an effective antitumor response independently since the immune system of a cancer patient is often compromised. Additional immunostimulation is often required to prompt the immune system to respond against residual or metastatic tumor cells.

3.2 Photochemical therapy combined with immune stimulation

ROS produced by PDT activate acute inflammation, increase tumor immunogenicity, and enhance T cell infiltration [96]. Immunostimulants can help to strengthen the immune response so that it can generate a potent anti-cancer effect. Immunostimulatory cytokines, such as granulocyte macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor-α (TNF-α), have shown significant therapeutic benefits in experimental studies when combined with PDT [97–98]. Granulocyte colony-stimulating factor (G-CSF) in combination with PDT to treat mouse colon cancer and non-small cell lung cancer resulted in enhanced neutrophil infiltration and activation causing tumor suppression and prolonged survival [99].

Other researchers have used different immunoadjuvants with complement activation to enhance the phototherapy-induced immune responses. Zymosan, an alternative complement pathway activator, in combination with PDT effectively increased the cure rate in animal models. In contrast, heat-aggregated gamma globulin, a classical complement pathway activator, did not increase the efficacy of PDT [100].

Microbial vaccines have also been used as effective immunoadjuvants for photo-immunotherapy. To treat mouse squamous cell carcinoma, a *Streptococcus* preparation, OK-432, in combination with PDT was used [101]. OK-432 used 3 hours prior to PDT could enhance the anti-tumor effect of PDT, while the treatment was not effective when OK-432 was used immediately after PDT. *Corynebacterium parvum* (C-parvum), a bacteriostatic vaccine, combined with phototherapy to treat bladder cancer-bearing mice indirectly stimulated the phagocytic cells and natural killer cells to achieve a better therapeutic effect [102]. Bacillus Calmette-Guérin (BCG) combined with PDT in the treatment of a breast cancer model, EMT6, also demonstrated that the combination therapy improved the cure rate over treatment without BCG [103].

The above studies using different types of immunostimulants have confirmed that the combination of phototherapy and immunotherapy provides a synergistic effect and have high clinical potential.

3.3 Photothermal therapy combined with immune stimulation

Laser immunotherapy (LIT), a combination of laser PTT and immunotherapy, was first proposed by Chen et al. [18]. LIT consists of three basic elements: an NIR laser, a photo-absorber, and an immunoadjuvant [104–105]. The photothermal effect of laser irradiation

directly causes local ablation of tumor tissue and the release of tumor antigens. Since all the antigens are derived from the patient's own tumor cells, the antigens provide targeted immunostimulation against the tumor. An immunoadjuvant, glycated chitosan (GC), is then used to induce a systemic anti-tumor immune response. As the residual tumor cells and untreated metastatic tumors are homologous to the treated tumor, the immune response attacks the remaining cancer cells. This approach allows the host immune system to sample a variety of tumor antigens in which to mount an effective immune response. Essentially, LIT results in *in situ* autologous cancer vaccine that can effectively treat late-stage, metastatic cancer [106].

By using the patients own tumor as the source of antigens *in vivo*, LIT can be considered as a personalized cellular therapy. Efforts to find ubiquitous tumor antigens among the patients with the same type of cancer have been largely failed, possibly as a result of each indivuals tumors being unique. LIT eexploits the tumor antigens of each individual patient undergoing treatment. Our preliminary studies indicate that LIT induced immunity is tumor specific, and autoimmunity does not appear. Several months after tumor clearance, treated mice appear healthy, but more work needs to be done to confirm autoimmunity is not occuring. It is well known that recurring cancer is often more aggressive, treatment- or drug-resistent, due to tumor cell mutation. LIT overcomes these challenges adequately, since it treats each tumor as a new target to expose a variety of unique antigens specific to the patient and specific to the recurring tumor.

Several preclinical studies have confirmed the potential of LIT in eliminating treated primary tumors and eradicating untreated distant metastases [107–108]. One study used an 805-nm laser combined with ICG and GC to treat DMBA-4 metastatic breast cancer in rats. The results showed that 38% of rats in the combination therapy group were long-term survivors, while all tumor-bearing rats in the control group died within 40 days [109]. The DMBA-4 tumor cell line used in this study is considered to be poorly immunogenic, and therefore LIT was thought to dramatically improve the immunogenicity of the tumor and induce tumor-specific immunity. Another study showed that LIT induced a long-term immunity to the tumor, with the cured rats resisting re-inoculation of the tumor cells [110].

4. Nano-photo-immunotherapy

Combining nanomaterials with photoimmunological therapy can significantly increase the treatment efficacy. Nanomaterials usually have some special physical and chemical properties or conjugate structures. Nanotechnology-based photoimmunological therapy can significantly increase the accumulation of nano-sized drugs in the target tumors [111]. During phototherapy, nanomaterials can enhance the anti-tumor immunity by releasing immune stimulants and other agents.

4.1 Nano-photochemical immunotherapy

Novel nanomaterials technology can be used to enhance PDT-based cancer treatments to more efficiently treat deeper tumors and enhance the immune response following treatment.

Kuangda et al. encapsulated small molecule immunotherapeutic agents that could inhibit indoleamine 2,3-dioxygenase (IDO) in a chlorin-based nanometallic organic framework (nMOF) [112]. This nanostructure was capable of inducing an anti-tumor immune response through PDT while delivering an indoleamine 2,3-dioxygenase inhibitor to the target tumor. The experimental results confirmed that the infiltration of T cells in the local microenvironment was significantly increased following treatment. Animal experiments using a colon cancer model showed that PDT utilizing this novel nanomaterial resulted in an effective systemic response, with reduction of both locally-treated tumors and distant metastases.

Similarly, zinc pyrophosphate nanoparticle that encapsulated the photosensitizer pyropheophorbide-lipid conjugate (ZnP@pyro) in combination with light irradiation, ZnP@pyro could directly induce tumor cell apoptosis and necrosis to enhance the immunogenicity of 4T1 tumor cells. Additionally, the ZnP@pyro nanoparticles in PDT increased the sensitivity of tumor cells to immune checkpoint inhibitors and had a significant inhibitory effect on primary tumors and lung metastases. Using bilateral 4T1 tumor models, researchers examined the therapeutic effect of ZnP@pyro in combination with light irradiation and PD-L1 antibody. The results showed that orthotopic tumors receiving local treatment were effectively cleared, whereas the growth of distant tumors without topical treatment was also inhibited. Thus, ZnP@pyro nanoparticle-mediated PDT enhances the systemic immune response following PDT.

4.2 Nano-photothermal immunotherapy

In PTT, the heat-killed tumor cells release specific antigens that are recognized by the body's immune system to produce an anti-tumor response. Recently, researchers developed synergistic nanosystems to further enhance the host anti-tumor immunity by the combination of nanoparticles and immunoadjuvants.

SWNTs can be used for the targeted destruction of sub-organelles and drug delivery during phototherapy therapy. Zhou et al. used fluorescent molecular markers to trace the interactions and subcellular localization of SWNTs under physiological conditions in real-time [114]. The results showed that SWNTs could cross the cell membrane of tumor cells, and eventually reside in the mitochondria (Figure 4). Using mitochondrial targeting SWNTs, photothermal [115] and photoacoustic [116] tumor cell destruction under laser irradiation through necrosis and apoptosis was achieved.

Taking advantage of the carrier nature of SWNTs, Zhou et al. conjugated the immunostimulant GC to SWNTs [29] (Figure 5). After irradiation with a 980-nm NIR laser, the tumor cells were killed by the SWNT-mediated photothermal effect. The damaged cells produced antigens, which were recognizable by the immune system. At the same time, GC is able to enhance tumor immunogenicity and trigger a stronger anti-tumor immune response. In animal studies, the results showed that the combination of phototherapy with SWNT-GC, not only effectively killed the local and metastatic tumors, but also produced an effective long-term anti-tumor immune response.

Tao et al. conjugated graphite oxide (GO), polyethylene glycol (PEG), and polyethyleneimine (PEI) together to use as a vector for immunoadjuvants [117]. GO-PEG-PEI could promote the production of proinflammatory cytokines and enhance the stimulating effect of immunoadjuvant CpG oligodeoxynucleotides (CpG ODN). Under laser irradiation, these nanoparticles produced local hyperthermia and accelerated intracellular transport of nanocarriers. *In vivo* experiments also demonstrated that the GO-PEG-PEI-CpG complex had synergistic photothermal and immunological effects for cancer treatment under laser irradiation.

Nanoparticles that encapsulates immunoadjuvant CpG ODNs in chitosan-coated CuS have also been used [118]. Unlike other sustained-release nanoparticles, this nanostructure decomposed under laser irradiation and converted to a new polymer which retained its immunostimulatory activity. While PTT releases tumor antigens, the stimulation of immunoadjuvants enhanced the specific anti-tumor immunity as demonstrated in studies on mouse breast cancer models. The proposed immunological mechanism is that DCs are activated by chitosan-coated CpG, leading to activated NK cells and the proliferation of cytotoxic T lymphocytes (Figure 6).

Other researchers have also combined nanoparticles with other immunostimulatory drugs. For example, Qian et al. linked the photothermal converter ICG to imiquimod (IMQ), a toll-like-receptor 7 agonist, by poly lactic-co-glycolic acid (PLGA) [119]. It is noteworthy that the PLGA-ICG-IMQ nanoparticles are formed by three clinically approved ingredients and therefore have a high potential for clinical application. The results showed that this new nanoparticle produced effective photothermal reaction under NIR laser irradiation, killed local tumor cells, and led to an effective immune response. The treatment can be further enhanced when combined with the checkpoint inhibitor, anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), to inhibit metastases (Figure 7).

Checkpoint inhibitors such as anti-CTLA-4 can increase the infiltration of T cells and reduce the regulatory T cells in tumor metastases. SWNTs combined with anti-CTLA-4 antibody and photoimmunotherapy confirmed that SWNTs could kill tumor cells and release tumor-associated antigens. The polyethylene glycol coating on SWNTs could also act as an immunoadjuvant in promoting the maturation and proliferation of DCs. Therefore, this combination could effectively enhance the immune response following photoimmunotherapy.

4.3 Antibody-targeted photodynamic therapy

Kobayashi et al. reported a unique method of targeted phototherapy [121]. They conjugated a photosensitizer, MAB-IR700, to a monoclonal antibody with the purpose of selectively binding the photosensitizer to the target cells. Use of NIR light irradiation effectively induced necrosis of the target tumor cells, while the damage to adjacent normal cells was limited.

Another study by the same group also found that the new antibody-photosensitizer was capable of simultaneously delivering nanoscale (10–200 nm) agents into the tumors. The combination of antibody-photosensitizer conjugate and phototherapy also caused an

immediate and significant increase in vascular permeability, a phenomenon known as “super-enhanced permeability and retention” (SUPR). They combined the antibody-photosensitizer conjugate with liposome-daunorubicin to achieve enhanced therapeutic effects and longer survival in mouse skin cancer [122].

5. Prospects

Phototherapy, immunotherapy, and nanomaterials represent three of the most important technological advancements during the past several decades. Immunotherapy has already been shown to hold great promise in cancer treatments, and the combination with phototherapy has shown strong pre-clinical promise to treat metastatic cancers. Nanomaterials can play a role to enhance the specific effects of both immunotherapeutic and phototherapeutic approaches to cancer treatments simultaneously.

NPIT based on either a photothermal or photochemical effect provides opportunities for novel approaches to cancer treatment with enhanced immune stimulation. For example, the laser-ICG-IMQ treatment produced T cells with increased quantity and quality and enabled an immunotherapeutic checkpoint inhibitor to effectively control the metastatic cancers, as demonstrated by a recent clinical study for melanoma treatment [123].

More and more experimental results are showing that the synergistic effects of nanotechnology-based phototherapy and immunotherapy may be key for the treatment of metastatic tumors. The combination of these three technologies shows strong promise to treat metastatic cancers using a localized treatment with minimal side-effects. However, the clinical value of NPIT still needs to be confirmed by further clinical control experiments. It is foreseeable that along with the continuous development of photonics, immunotherapy, and nanotechnology, NPIT will only continue to improve.

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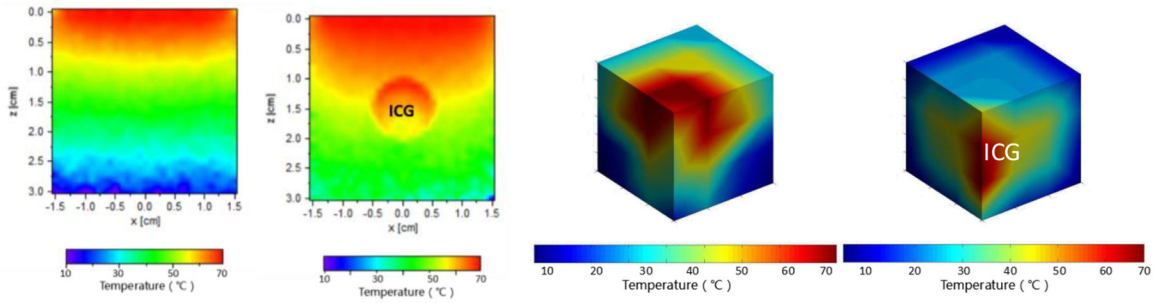

Figure 1.

Two-dimensional and three-dimensional schematic diagrams of selective photothermal effect with and without light a light absorber (ICG) [46] Copyright © 2002, Springer Nature.

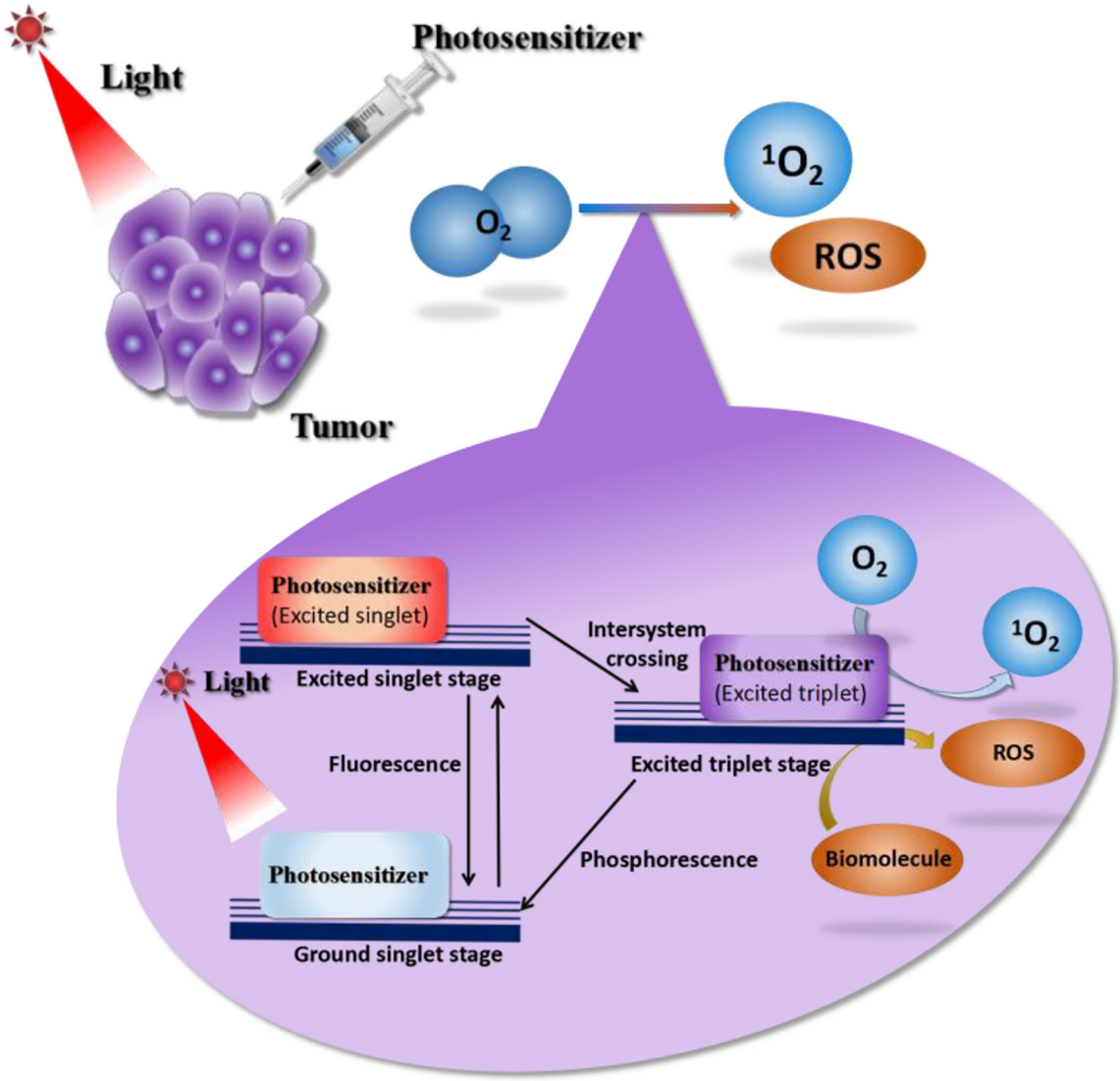

Figure 2.

Schematics of PDT.With advances in nanomaterials technology, more innovative photosensitizers have been developed for PDT. For example, up-conversion nanoparticles can convert NIR light into UV-visible light [74], and scintillating nanoparticles can be excited by X-rays to achieve an effect in deep tissues [75]. With the special characteristics of these nanomaterials, PDT can be activated by more deeply penetrating radiation.

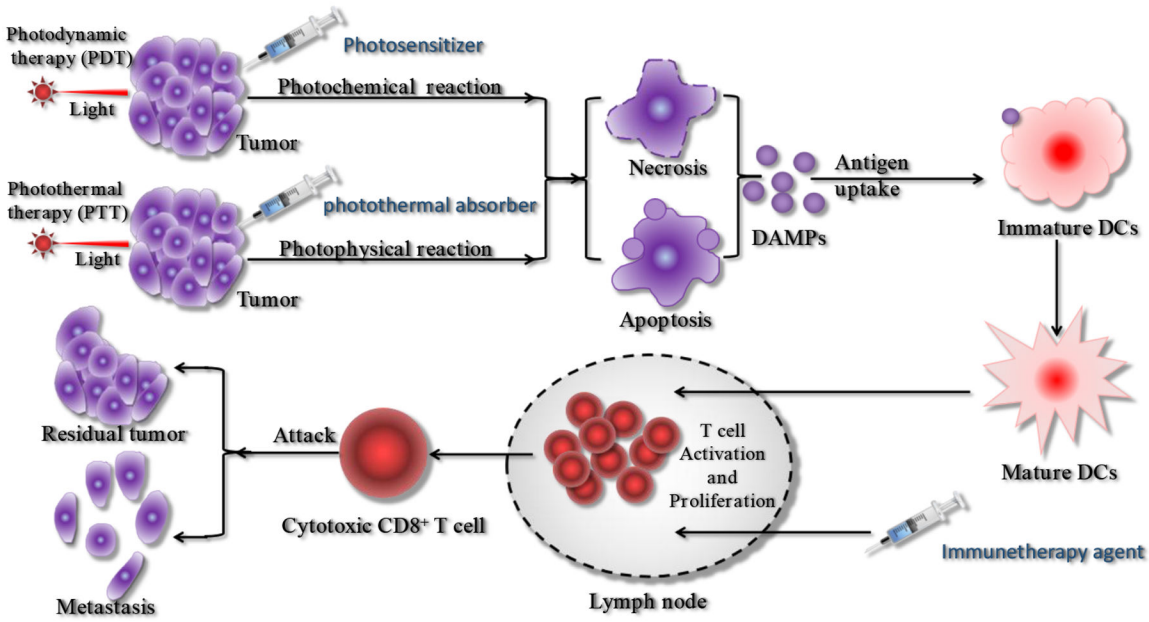

Figure 3.
Schematics of the basic principles of photoimmunological therapy.

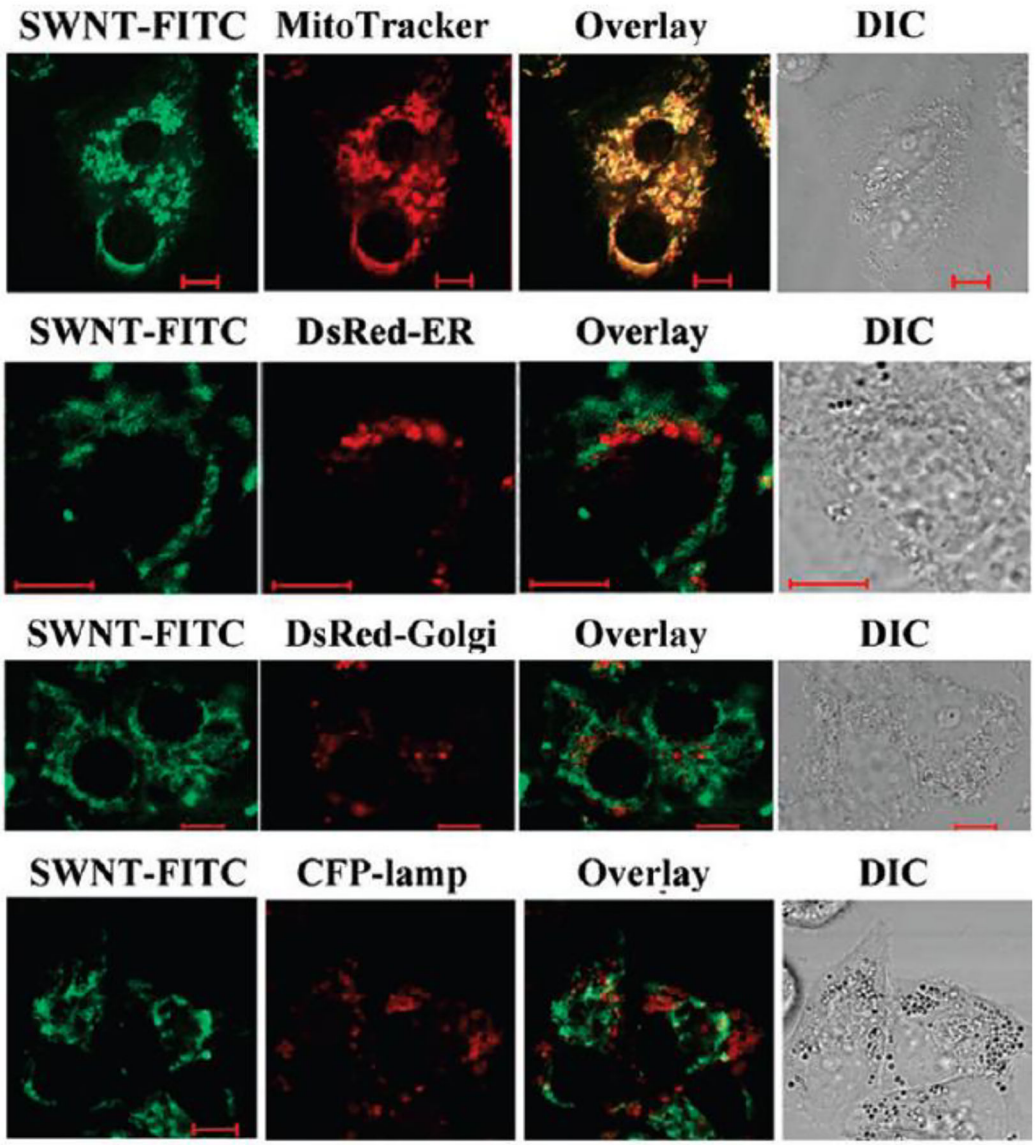

Figure 4.

Confocal images of the tumor cells show that SWNT-PL-PEG-FITC is localized in the mitochondria of the tumor cells [114] Copyright. 2010, American Chemical Society.

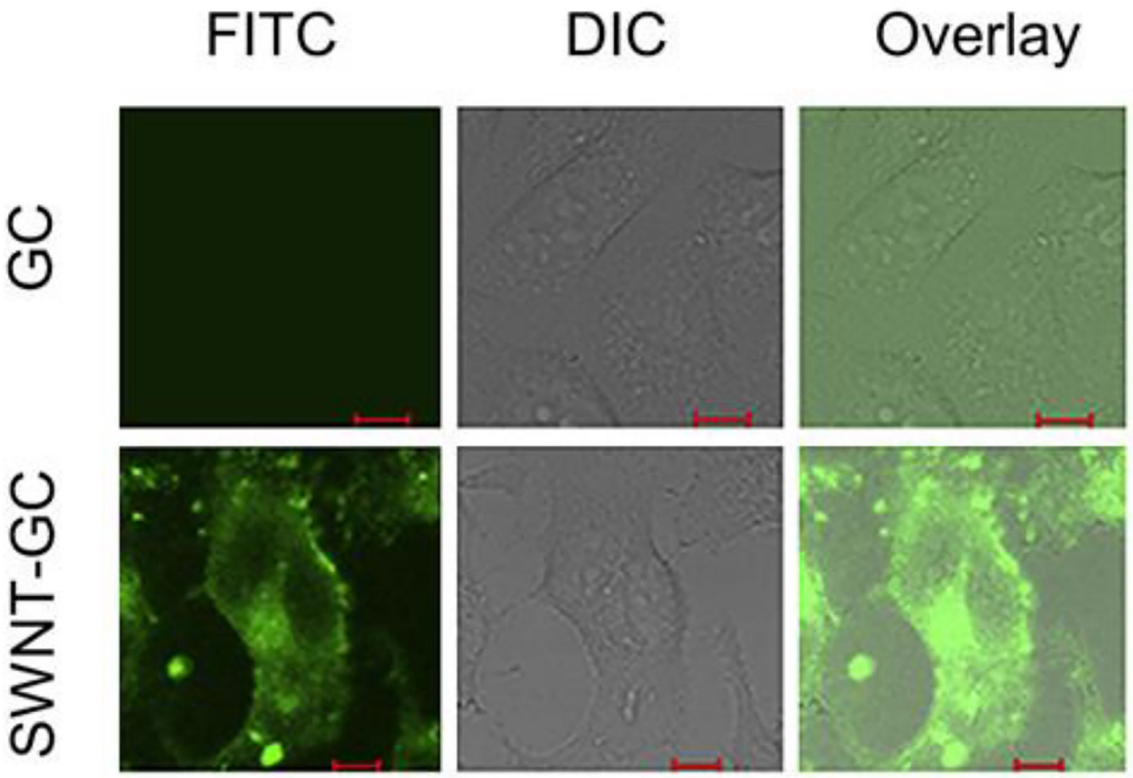

Figure 5.
Fluorescent images of SWNT-GC-FITC and GC-FITC in EMT6 cells showed that GC could enter tumor cells when conjugated with SWNTs [29] Copyright © 2011 Elsevier Ltd.

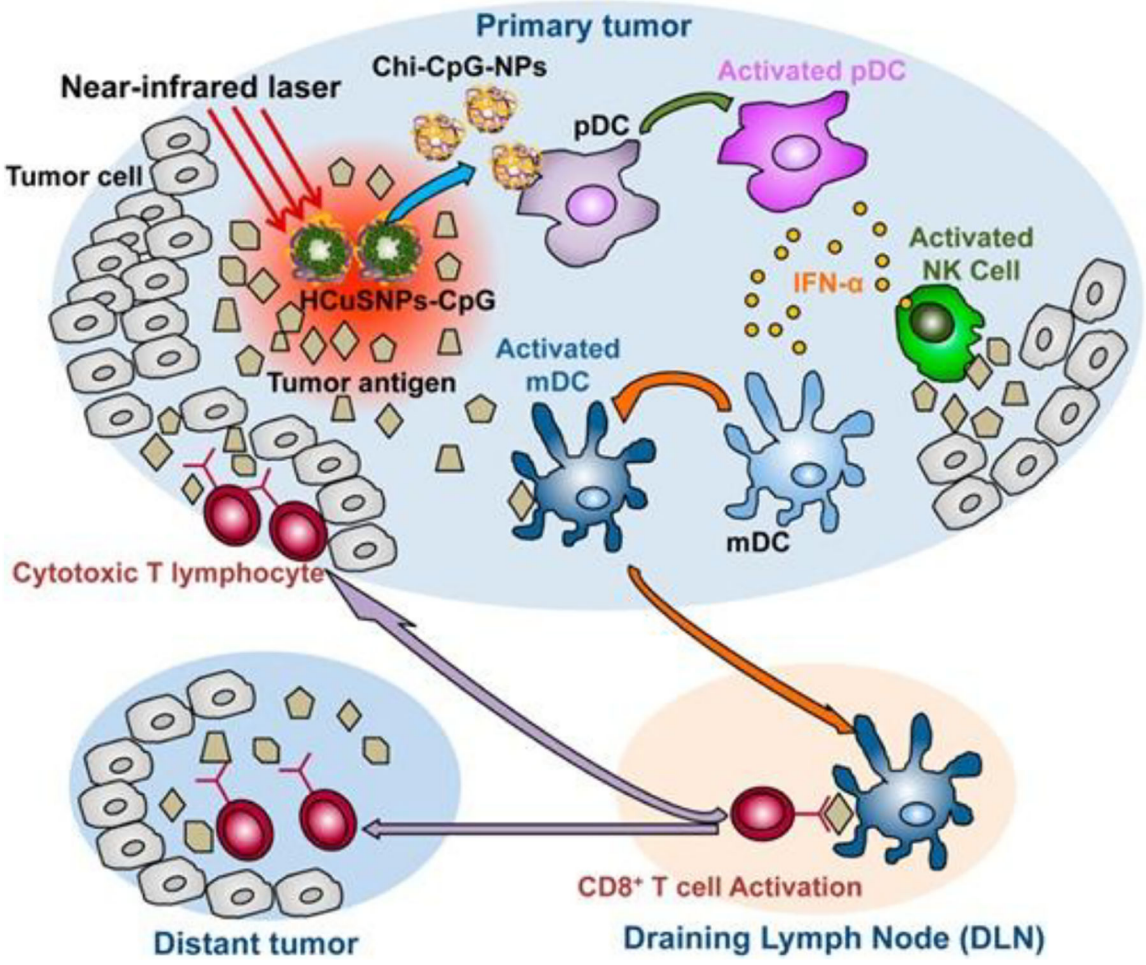

Figure 6.

Schematics of combined photothermal and immunotherapy using chitosan-coated hollow copper sulfide nanoparticles [118] Copyright © 2014 American Chemical Society.

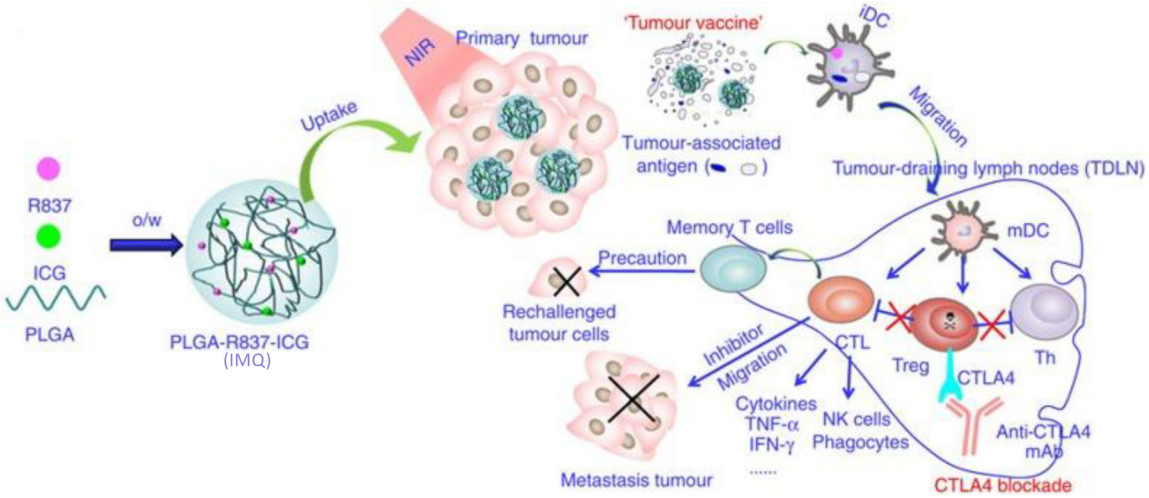

Figure 7.

Schematic diagram of PTT with immune-adjuvant nanoparticles together with anti-CTLA-4 [119] Copyright © 2016, The Author(s).