Nanoparticles for Thermal Cancer Therapy

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Advances in nanotechnology are enabling many new diagnostic and therapeutic approaches in cancer. In this review, examples where nanoparticles are employed to induce localized heating within tumors are explored. Approaches to nanoparticle-mediated thermal therapy include absorption of infrared light, radio frequency ablation, and magnetically-induced heating. These approaches have demonstrated high efficacy in animal models, and two are already in human clinical trials.
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1 Introduction

Over the past 50 years, despite tremendous advances in our knowledge of the genetic, molecular, and cellular underpinnings of cancer, there has been no change in the age-adjusted mortality from cancer [1]. Cancer remains the second leading cause of death in the United States, accounting for over 25% of the deaths in the population. More than one million cases are diagnosed each year, resulting in over 500,000 deaths [2]. Current strategies for cancer therapy are based primarily on surgical excision and medical approaches such as chemotherapy and radiation, often in combination. Surgery often fails to remove all cancerous cells and is associated with significant morbidity; further, a large number of tumors are classified as inoperable due to their adjacency to critical tissue structures. The destruction of solid tumors using hyperthermia has been under investigation for some time. Hyperthermia can lead to cell death through such mechanisms as protein denaturation or rupture of the cellular membrane. Cancerous cells are subsequently removed by macrophages, causing the tumor to shrink. Previously investigated thermal therapies have employed a variety of heat sources including laser light [3–5], focused ultrasound [6], and microwaves [7]. The benefits of thermal therapeutics over conventional resection are numerous; most approaches are minimally noninvasive, relatively simple to perform, and have the potential of treating embedded tumors in vital regions where surgical resection is not feasible. However, in order to reach underlying tumors or to treat large tumors, the activating energy source must sufficiently penetrate healthy tissues. Unfortunately, simple heating techniques have trouble discriminating between tumors and surrounding healthy tissues, and often heat intervening tissue between the source and the target site. Thus, numerous groups are investigating the use of energy-absorbing agents localized within tumor tissues to facilitate localized heating. In many cases, nanoparticles provide unique energy absorption properties as well as appropriate biodistribution for these applications.

2 Near-Infrared Photothermal Therapies

Photothermal interactions result from light energy conversion to heat within the tissue, potentially providing the sustained elevated temperatures required for hyperthermia therapies [8]. Photothermal damage is characterized by mitochondrial swelling, protein denaturation, loss of birefringence, edema, whitening, and tissue necrosis. Tissue changes are evident within minutes when temperatures reach 55–95°C [9,10]. The primary absorbers in tissue are water, hemoglobin, oxyhemoglobin, and melanin. Light absorption by these components can lead to photothermal tissue damage, but it is generally difficult to discriminate between normal and diseased tissues via these mechanisms. Absorption of light is minimal in a near-infrared region (NIR) between approximately 700 nm and 900 nm [11], as this region is above the hemoglobin absorption bands and below where absorption by water becomes significant. Thus, these wavelengths induce minimal heating in normal tissues. However, if an exogenous absorber can be introduced to the diseased tissue, NIR light can cause photothermal destruction of the targeted diseased tissue with minimal damage to intervening normal tissue.

Near-infrared absorbing gold nanoshells have been extensively investigated for NIR photothermal therapy, with phase I human clinical trials ongoing. Nanoshells consist of a spherical dielectric core nanoparticle encapsulated by an ultrathin metal shell. The ratio of core radius to shell thickness dictates the scattering and absorbing properties of the particle. For a given core radius, decreasing the shell thickness (increasing the core:shell ratio) shifts the peak plasmon resonance to longer wavelengths (Fig. 1). Peak resonance can be controllably placed in the near-infrared region [12,13].

Nanoshell photothermal cancer therapy works through the preferential accumulation of nanoshells in a tumor and absorption of NIR light by those particles to locally generate heat at the tumor site. Nanoshells have been shown to passively accumulate in tumors after intravenous injection [14,15] as a result of the leaky vasculature characteristic of neoplastic tumors [16]. After systemic injection and accumulation at the tumor site, NIR light is applied over the tumor region. The absorbed energy causes the nanoshells to heat, allowing local destruction of the tumor tissue. In a mouse model, nanoshell-treated tumors completely regressed after NIR illumination ($4\ W/cm^2$ for 3 min) without tumor regrowth [15]. The tumors receiving the nanoshell therapy experienced rapid temperature rises sufficient to cause irreversible tissue damage (temperatures of 50°C were achieved within 30 s from the start of laser irradiation), while laser application to nearby healthy tissue or to tumors not treated with nanoshells did not induce a significant temperature increase [17], as shown in Fig. 2. The preferential accumulation and absorption minimizes damage to surrounding tissues. Biodistribution studies in tumor-bearing mice have shown that systemically-delivered nanoshells coated with poly(ethylene glycol) are found mainly in the spleen, liver, and tumor [14]. Additionally, nanoshells can be easily modified with targeting agents, such as antibodies, to further improve the specificity of the therapeutic approach [18,19].

While nanoshells are attractive for NIR thermal therapy, this approach can be accomplished with any nontoxic, NIR-absorbing material. Some of the other materials that have been recently investigated include gold nanorods [20,21], gold nanoclusters [22,23], gold nanocages [24], and hollow gold nanoshells [25]. Gold nanorods are the most extensively studied of the other nanoparticle formulations, and they are attractive for use in photothermal therapy because they are efficient absorbers of near-infrared light and they are smaller than nanoshells (nanorods are $\sim 10 \times 50\ nm^2$ compared to nanoshells which are ~ 150 nm in diameter). Gold nanorods have not been widely used in biological applications due to concerns about the toxicity of a surfactant used

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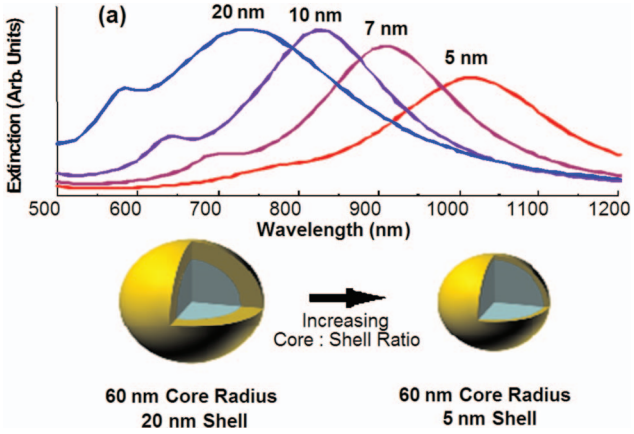

Fig. 1 Varying thicknesses of gold shells upon silica core nanoparticles provide formulations with tunable optical properties. Near-infrared absorbing particles can be easily fabricated.

in the particle synthesis, hexadecyltrimethylammonium bromide (CTAB), which is known to degrade membranes and peptides. Various schemes have been employed to reduce the levels of CTAB present on particles before their use in vivo. A biodistribution study on nanorods coated with poly(ethylene glycol) showed that most of the particles are found in the liver following systemic injection into mice [26].

3 Magnetic Fluid Hyperthermia

Magnetic nanoparticles are also being investigated for use in thermal treatment of cancer. In magnetic fluid hyperthermia (MFH), magnetic nanoparticles are delivered to a tumor either intravenously or through direct injection. This is followed by application of an alternating magnetic field that causes the particles to heat. As the temperature rises in nearby cancerous cells, they are eradicated due to rupture of the cellular membrane or denaturation of proteins. It has also been postulated that an immune response may be stimulated to destroy remaining tumor cells [27]. The heating phenomenon of magnetic materials was first investigated by Gilchrist et al. in 1957 [28]. Of the materials tested, iron oxide particles were the most promising, and they demonstrated no adverse effects on tissue when delivered into the lymph nodes of dogs. Since these initial studies, the biocompatibility of iron oxide nanoparticles has become well established, and they have remained the most thoroughly investigated agent for MFH.

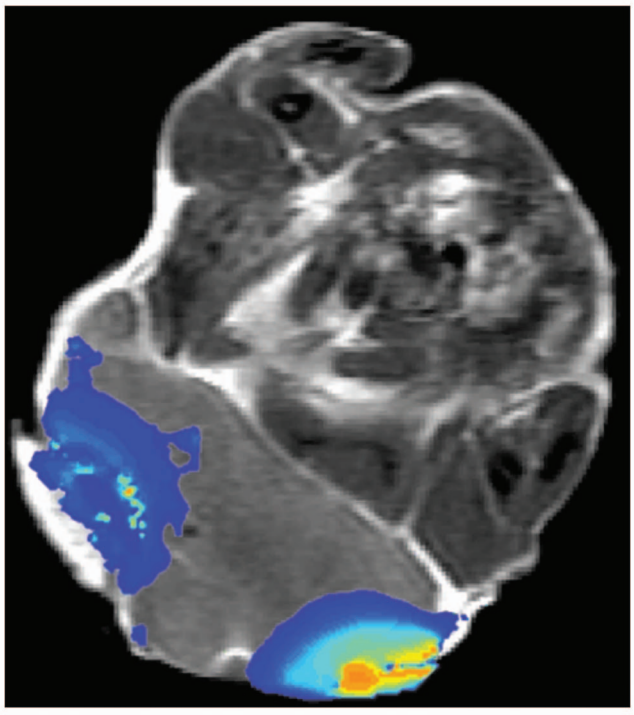

Fig. 2 Magnetic resonance thermal imaging was used to measure temperature profiles in nanoshell-treated tumors during NIR illumination. Both tumor sites underwent rapid heating, while the normal tissue in between did not experience a significant change in temperature.

The process of heat generation by magnetic nanoparticles less than 20 nm in diameter has been attributed to a combination of Néel and Brownian relaxations, which are rotation of the magnetic moment within a nanoparticle or of the entire nanoparticle within its surroundings, respectively [29,30]. In the presence of an alternating magnetic field, the magnetic moment of a particle changes orientation to align with the field. As the particle moment returns to its equilibrium position, the magnetic energy dissipates as thermal energy [29]. Brownian heating is a result of frictional losses associated with particle movement in low-viscosity fluids. Experimentation has indicated that the heating power of ferrofluids depends on the particle size, surface coating, and strength of the applied field [29–31]. Currently the best particle formulations have a loss power of ~200 W/g in a 14 kA/m field (f =300 kHz) [29]. In vivo temperatures of ~55°C have been achieved when up to 0.5 ml/cm^3 tumor volume of magnetic fluid (120 mg iron/ml) were injected into rat prostates and a 12.6 kA/m magnetic field was applied [32].

Experimental results for magnetic fluid hyperthermia with iron oxide nanoparticles have been promising. In 1981, Rand et al. [33] published studies of MFH treatment of renal carcinoma in rabbits, reporting that sustained heating of tumors to 50°C over 10–15 min is more effective than cyclic heating to 55°C. Additionally, Hilger et al. [34] used in vivo breast cancer models to show that particles should be evenly dispersed throughout the tumor to ensure adequate heating and total tumor destruction. To encourage tumor targeting and even tissue distribution of iron oxide nanoparticles, various schemes have been employed, such as coating the surface with antibodies. It has been demonstrated that anti-HER2 coated iron oxide binds more specifically to SK-BR-3 human breast carcinoma cells and causes the cells to experience larger temperature increases when exposed to a magnetic field (410 kHz, 11 kA/m) than particles coated with a nonspecific probe [35]. Another mechanism that has been developed to increase tumor uptake of iron oxide particles is to encapsulate them inside liposomes, which may also be conjugated to antibodies for further targeting enhancement [36–38].

Recently, the first two clinical studies regarding magnetic fluid hyperthermia were published [32,39]. In the first, a 67 year-old patient with prostate cancer received direct tumor injection of 12.5 ml aminosilan-coated iron oxide nanoparticles. Following the injection, the patient was subjected to an alternating magnetic field (100 kHz, 4–5 kA/m) once weekly for 6 weeks. The results of this study indicated that the nanoparticles were retained in the prostate for the entire 6 week period. In addition, the feasibility of the technique and the ability to obtain temperatures satisfactory for ablation of tumor cells were proven, as seen in Fig. 3 [32].

The second clinical report was a feasibility and tolerability study on 14 patients with glioblastoma multiforme [39]. Patients were treated for 6 weeks with a combination of external beam radiotherapy and MFH using aminosilane-coated iron oxide nanoparticles injected directly into the tumor with assistance of navigational controls. The appearance of iron oxide particles in the tumor can be appreciated in the postinjection computed tomography image shown in Fig. 4. In this study, the magnetic field applied had a frequency of 100 kHz, and the therapy was well tol-

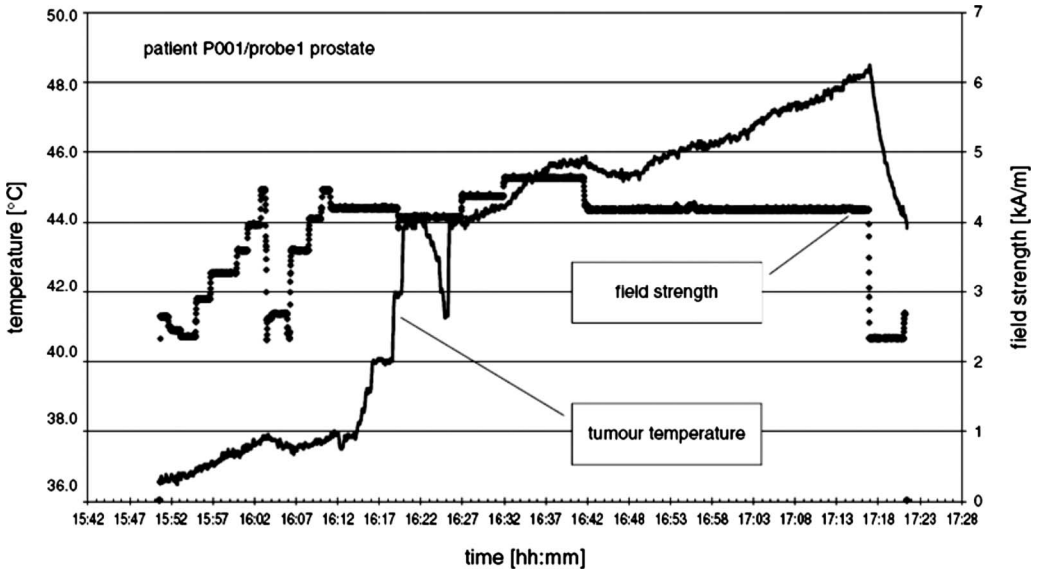

Fig. 3 Temperature inside the prostate and magnetic field strength plotted versus time during the course of magnetic fluid hyperthermia. The thermocouple was moved through the tumor to find the position with maximum temperature, where it was left for the remainder of the session. The downward spike in temperature indicates the border of the prostate. Temperature increased until the magnetic field was removed, at which point the temperature dropped rapidly ([32], with permission from Taylor & Francis Group, http://www.informaworld.com).

erated at magnetic field strengths ranging from 3.8 kA/m to 13.5 kA/m. Overall the findings indicate that MFH does not cause any adverse effects on patients, and future studies need to be performed to determine the efficacy of the treatment.

4 Radiofrequency Ablation

Another type of nanoparticle-based thermal therapy relies on the administration of radiofrequency (rf) irradiation. Radiofrequency ablation (RFA) occurs when an electrode inserted into a tumor applies a rf current, which induces agitation of the ions within the tissue, leading to frictional heating [40]. The heating rate of the tissue is related to the specific absorption rate (*SAR*) and is described by the equation

$$HR = \frac{SAR}{69.77 C_H} \tag{1}$$

where C_H is the specific heat capacity of the tissue (kcal/kg °C). *SAR* (W/kg) is described by

$$SAR = \frac{\sigma}{\rho} E^2 \tag{2}$$

where σ is the dielectric conductivity of the tissue, ρ is the density of the tissue, and E is the root-mean-square value of the resulting electric field strength in the tissue [41]. The conductivity properties of gold nanoparticles (GNPs) and single-walled carbon nanotubes (SWNTs) provide the possibility of more efficient heating under rf field exposure and are thus explored in the use of RFA of

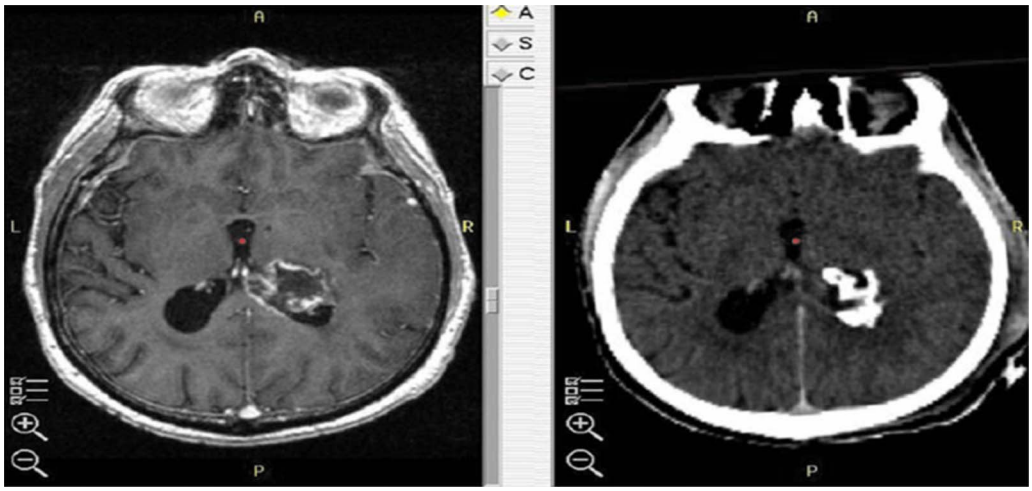

Fig. 4 Left image: preoperative magnetic resonance image displays the location of the tumor in the right posterior horn of the ventricle; right image: postoperative CT verifies magnetic nanoparticle accumulation in the tumor ([39], Fig. 1, with permission from Springer Science+Business Media).

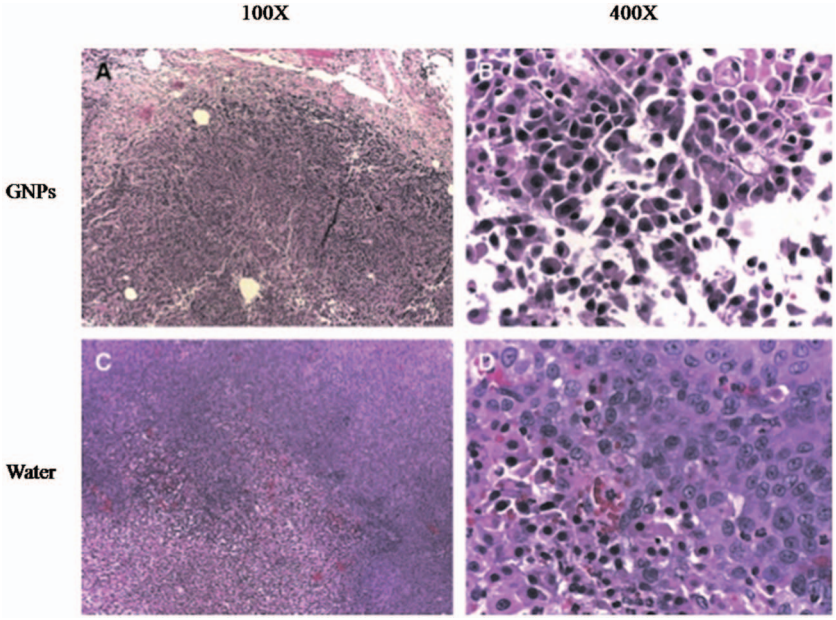

Fig. 5 H and E staining reveals a greater presence of tissue necrosis in tumors receiving GNPs before rf field exposure than those receiving water only ([42], with permission from Elsevier).

tumors. The use of nanoparticles seeks to improve the current rf ablation by increasing specificity of treatment to the tumor site and providing a noninvasive method of therapy. It has been shown that the presence of GNPs within a tumor significantly increases the temperature experienced by the tissue upon exposure to rf energy. The extent of increase in temperature is dependent on the power of the rf field [42]. The rate of heating has been shown to increase with a higher concentration of gold nanoparticles with 67 μM GNPs heating to 90°C after 5 min and 1.1 μM GNPs heating to 25°C after 5 min of heating in a 200 W rf field [43]. The increased heating provided by the GNPs under exposure of a rf field leads to tissue destruction within a tumor. Cardinal et al. [42] demonstrated this through exposing tumor-bearing rats to a rf field following the injection of GNPs or water into the tumor. Hematoxylin and eosin (H and E) staining of tumor sections revealed that those tumors receiving an injection of gold nanoparticles sustained necrosis consistent with thermal injury (Fig. 5).

The heating induced by the application of rf can also be enhanced through the use of SWNTs, which is possible due to their resistive conductivity among other electrochemical properties [44]. As with gold nanoparticles, the rate of heating is dependent upon the concentration of the SWNTs. Gannon et al. [43,44] demonstrated the use of SWNTs in vivo to enhance rf field-induced heating by exposing tumor-bearing rabbits to a rf field following the direct injection of SWNTs into the tumor. Histological evaluation of the tumors revealed cellular necrosis in those tumors receiving SWNTs.

When comparing the heating rates under rf field exposure, GNPs seem to provide a more efficient system over SWNTs. Upon exposure to a rf field of 600 W, GNPs at a concentration of 67 μM (11.19 mg/L) experienced a temperature increase of 80°C after 2 min of rf exposure, while SWNTs at a concentration of 250 mg/L, ~22-fold that of the GNPs, experienced a temperature increase of only 33°C after 5 min of rf field exposure [43,44]. This suggests that gold nanoparticles may be better conductors of rf energy than SWNTs and may provide a better application for rf tumor ablation.

rf energy has been shown to penetrate tissue more deeply than near-infrared light. At 220 MHz, rf penetration is 7 cm and increases to 17 cm at 85 MHz, revealing an increase in penetration with a decrease in frequency [45]. Since near-infrared light only penetrates ~1 cm into the tissue, it is only applicable for subcutaneous tumors. This property suggests a potential broader clinical application of noninvasive RFA than NIR-photothermal ablation.

5 Conclusions

Thermal therapies are attractive for cancer therapy as this physical approach avoids concerns with drug resistance and biological variability between tumor types. Direct heating therapies have demonstrated moderate success, but have been limited by damage to normal tissue in addition to the tumor. The application of exogenous absorbers to the tumor tissue can allow more precise heating of the tumor site, reducing damage to normal tissue and enabling noninvasive therapy. In many cases, nanoparticles can be designed to generate local heating within a tumor site. In addition, nanoparticles can offer the opportunity to develop multifunctional platforms for integrated imaging and therapy [46,47].

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