



Gold nanostructures absorption capacities of various energy forms for thermal therapy applications

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ARTICLE INFO

Keywords:

Gold nanostructures
Ultrasound
Magnetic field
Electric field
Near infra-red exposure

ABSTRACT

This mini-review has investigated the recent progress regarding gold nanostructures capacities of energy absorption for thermal therapy applications. Unselective thermal therapy of malignant and normal tissues could lead to irreversible damage to healthy tissues without effective treatment on target malignant tissues. In recent years, there has been a considerable progress in the field of cancer thermal therapy for treating target malignant tissues using nanostructures. Due to the remarkable physical properties of the gold nanoparticle, it has been considered as an exceptional element for thermal therapy techniques. Different types of gold nanoparticles have been used as energy absorbent for thermal therapy applications under several types of energy exposures. Electromagnetic, ultrasound, electric and magnetic field are examples for these energy sources. Well-known plasmonic photothermal therapy which applies electromagnetic radiation is under clinical investigation for the treatment of various medical conditions. However, there are many other techniques in this regard which should be explored.

1. Introduction

Nanotechnology-based cancer hyperthermia provides new opportunities for cancer treatment. In this approach, nanoparticles should be injected to the body systematically, due to the effect of “enhanced permeation and retention”, or EPR (Greish, 2010), they tend to be accumulated in tumor tissues. Then, external energy sources are applied to heat up individual cancerous cells using nanoparticles which are considered as submicron energy absorbent. In theory, a variety of Nano materials and energy sources are applicable; in practice, however, there are many problems in this regard. Biocompatibility and toxicity of exerted nanoparticles, specific cancerous cell accumulation, sufficient heat generation, dispersed heat distribution and many other factors prevented some types of theoretically-viable Nanomaterial for nanoparticles mediated hyperthermia application.

Extraordinary gold nanostructures have been studied for several hyperthermia concepts through different energy sources. These particles are characterized by intense surface plasmonic resonance (SPR) (Shaabani et al., 2017), high thermal conductivity (Chol and Estman, 1995) and a unique super atom structure (McCoy et al., 2013) which lead to high absorption of light, electric and magnetic field. Compared to other nanostructures, gold nanoparticles show higher chemical stability and lower toxicity (Fadeel and Garcia-Bennett, 2010). In addition,

they are synthesized and conjugated to other biomolecules or nanostructures easily (Zarchi et al., 2018a). Here we present a mini review of gold nanostructures absorption capacities of various energy forms for possible thermal therapy applications.

2. Thermal therapy by gold nanoparticles through ultrasound absorption

Clinical and experimental ultrasound hyperthermia is carried out typically using high intensity focused ultrasound (HIFU). Even equipped HIFU system is applicable for large tumor volumes (Ho et al., 2011). Recently some inorganic Nanomaterial was applied as a heat generator under ultrasound exposure, albeit rather slowly. The physical mechanism of heat generation of an inorganic material such as metal and metal oxide nanoparticles under ultrasound exposure is unclear. However, the predicted results provide some hints. First, ultrasound attenuation coefficient of the acoustic wave was increased in the presence of nanoparticles in a medium (Sviridov et al., 2013). Second, metallic nanoparticles such as gold are regarded as great heat conductors which could influence the distribution of the adsorbed energy through the tumor volume (Chol and Estman, 1995), and finally, smaller gold nanoparticles can take the role of nucleation in the cavitation process and decrease the cavitation threshold (Farny et al.,

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<https://doi.org/10.1016/j.jtherbio.2018.12.007>

Received 15 August 2018; Received in revised form 4 October 2018; Accepted 9 December 2018

Available online 10 December 2018

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2005). Ultrasound cavitation plays an important role in the dissipation of energy in the exposed environment (Zarchi et al., 2018b). Wen et al. reported a significant heat generation of an ultrasound exposed medium containing gold nanoparticle (Wen, 2013). A comparative study which was conducted by Biek et al. investigated the sonosensitizing properties of different inorganic nanoparticles such as gold, iron oxide and graphene oxide nanoparticles. The heat generation rate of gold nanoparticles represented a superior efficiency compared to the other two nanoparticles which were both in the medium (Beik et al., 2016a) and this has been showed in vivo studies (Beik et al., 2016b). Few other cancer hyperthermia studies have been carried out on gold nanoparticles mediated hyperthermia. Brazzale et al. showed higher KB cancerous cell death by exploiting gold nanoparticles and ultrasound simultaneously compared to applying only one of the treatments (Brazzale et al., 2015). Similar results were obtained from different cancerous cells such as for A549, MDA-MB231 (Tarapacki and Karshafian, 2015) and Hela cells (Kosheleva et al., 2016). Qian et al. achieved a simple method regarding combination of ultrasound imaging and thermal therapy using gold nanoparticles coated PLGA (lactic-co-glycolic acid) capsules in bovine livers (Xi et al., 2015). Gold nanoparticle coated silica capsule (Wang et al., 2013) and gold nanoparticles coated adenovirus (Mo et al., 2015) were also capable to absorb energies through ultrasound imaging and thermal ablation similar to gold nanoparticles coated PLGA capsules.

3. Thermal therapy by gold nanoparticles absorption through electromagnetic radiation

Plasmonic photothermal therapy is not the only application of gold nanoparticles absorption of electromagnetic radiation. Researchers in biomedical science have investigated the interaction of different spectrum of electromagnetic radiation with gold nanoparticles frequently. These interactions are used for many applications, such as developing radiation absorbers for X-ray diagnostic and therapy application (Khademi et al., 2018), colorimetric sensors and diagnostic methods (Fatemi et al., 2017; Emami et al., 2015; Esmaeili-bandboni et al., 2017), photosensitizer for photodynamic therapy application (Darabpour et al., 2017; Amini et al., 2013) and many others.

Surface Plasmon Resonance (SPR) is a coherent and collective resonant oscillation of conduction electrons of metal nanoparticles, which are excited by the electric part of the light. This phenomenon leads to a very efficient heat generation at its maximum intensity which is known as plasmonic photothermal therapy. Gold nanoparticles, gold Nano rods and gold Nano shells can be prepared easily through wet chemical methods and can represent SPR absorption in a NIR (Near Infra-Red) spectrum of electromagnetic radiation. Therefore, these three nanostructures have been examined comprehensively in plasmonic photothermal therapy investigations (Huang et al., 2008). Other gold nanostructures such as Nano cages (Chen et al., 2010), Nano stars (Liu et al., 2015), and Nano prisms (Pérez-Hernández et al., 2014) were also a promising heat generator through NIR exposure. However, NIR electromagnetic light represents a low depth of tissue penetration for reliable hyperthermia and limits the utility of the technique (Larson et al., 2007).

Different aspects of gold nanostructures application in plasmonic photothermal therapy have been reviewed comprehensively by many experts (Huang et al., 2008; Kennedy et al., 2011). Here, we reviewed related clinical and preclinical reports. Gold Nano shells- based plasmonic photothermal therapies are applied in to clinical trial studies in the past decade. PEGylated gold Nano shells formulation which are titled AuroShell® particles (Nano spectra Biosciences Inc., Texas) has been evaluated in a series of phase I clinical trials, for photothermal therapy of the head and neck (NCT00848042), prostate (NCT02680535) and lung tumors (NCT01679470). The first two studies were completed but the last study was terminated. Based on these clinical trial studies Stern et al. confirmed the safety profile of

PEGylated gold Nano shells -based plasmonic photothermal therapy (Stern et al., 2016). Phase II clinical study of gold Nano shells has also investigated for photothermal therapy of coronary atherosclerosis treatment (NCT01270139). The analysis of this clinical follow-up is very promising for decreasing the risk of cardiovascular death (Kharlamov et al., 2015). Also, a clinical trial of stem cells containing gold nanoparticles with silica-iron oxide shells for plasmonic photothermal treatment of atherosclerosis was terminated under the political pressure (NCT01436123). The El-Sayed group examined the feasibility of gold Nano rod -based plasmonic photothermal therapy for spontaneous tumors in the mammary glands of canine and felines (Ali et al., 2016). Up to now, other gold nanostructures have not been investigated in clinical studies yet they and have been reported only in laboratory studies. Despite the clinical progress, gold nanostructure mediated photothermal therapy is still in its early stages.

4. Thermal therapy by gold nanoparticles absorption through electric field

John Kanzius was the owner of Radio Station Company who was diagnosed with leukemia. Kanzius introduced a non-invasive radio-frequency instrument (13.56 MHz, 1000 W) that was utilized by medical researchers quickly. In the early studies on Kanzius's machines, the cancerous cells or animal cancer models were treated by gold nanoparticles and were irradiated through radio frequency electric field (RF-EF) (Cardinal et al., 2008; Schmidt, 2008). In the first fundamental investigation of the gold nanoparticles heating profile was reported as the main effective heating mechanism under RF-EF exposure, inductive or Joule-type heating of gold nanoparticles in aqueous solution (Moran et al., 2009). But the novelty of the technique overshadowed some neglected factors on Joule heating mechanism that leads to an over-estimation of gold nanoparticles' heating behaviors in RF-EF energy field, which puts into question the whole idea both theoretically (Hanson et al., 2011) and experimentally (Li et al., 2011). Subsequently, two independent groups introduced the electrophoretic mechanism for observed heating of RF-EF exposed to gold nanoparticles both in practice (Corr et al., 2012) and in theory (Sassaroli et al., 2012). Electrophoretic movements of charged nanoparticles are dominant for particles which are smaller than 10 nm in diameter (Corr et al., 2012).

In addition to the size of the gold nanoparticles, our study shows the importance of surface charge and surface chemistry of gold nanoparticles in the observed heating response. Gold nanoparticles which have been stabilized by charged molecules such as CTAB (Cetrimonium bromide), were a better heat generator compared to those which have been stabilized by natural long-chain PEG (Poly ethyl glycol) (Amini et al., 2017). We also evaluated the small mercapto succinic capped gold clusters (2 nm size) for in-vitro RF-EF hyperthermia experiment. Due to very small size and dense charged surface, gold clusters show a higher heating rate compared to bigger nanoparticles. Surface charge and small size are factors influencing the electrophoretic motions of nanoparticles in the electric field (Amini et al., 2017).

5. Thermal therapy by gold nanoparticles absorption through magnetic field

Applying alternative magnetic fields for magnetic nanoparticles mediated hyperthermia is a well-known procedure that have been investigated remarkably in clinical studies (NCT02033447). However, gold is not magnetic. For the first time, the concept of “super atom” has been used for extraordinary ferromagnetism and paramagnetism characteristic of small gold clusters (McCoy et al., 2013; Walter et al., 2008). The oxidation state of gold cluster super atom is critical for observed magnetic behaviour (Tofanelli and Ackerson, 2012; Zhu et al., 2009) magnetic heating of tailored gold Nano clusters through Brownian and Néel relaxation mechanisms (McCoy et al., 2013; Nealon et al., 2012). Schifferli et al. reported the controllable DNA hybridization

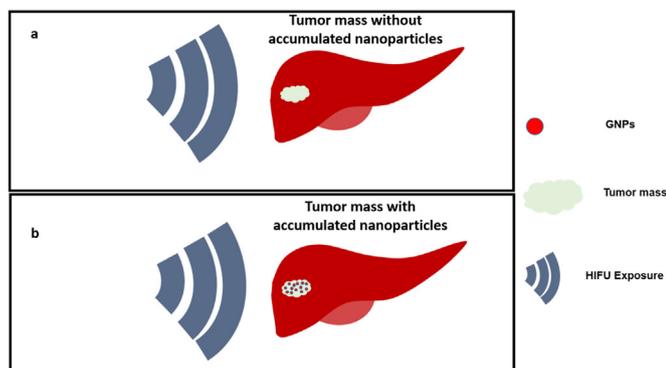


Fig. 1. Schematic view of HIFU mediated thermal therapy. a) In classical HIFU mediated thermal therapy, the HIFU exposure would absorb tumor volume and normal tissue similarly in the exposed area. b) However, in gold nanoparticles mediated HIFU thermal therapy, gold nanoparticles accumulated in the liver tumor can influence HIFU mediated thermal therapy through three different mechanism which is: (1) better heat distribution in tumor mass, (2) Intensified cavitation process in tumor mass and (3) higher ultrasound attenuation coefficient in tumor mass.

through employing DNA strands conjugated with gold Nano cluster (1.4 nm) and 1 GHz magnetic field exposure (Hamad-Schifferli et al., 2002). In a similar study which was conducted by Gupta et al., an increase in the temperature was recorded in the vicinity of 1.4 nm gold Nano clusters, when exposed to an alternative magnetic field, through small fluorescent quantum dots (Gupta et al., 2010). There are some others follow up on this technique (Taira et al., 2011; Wijaya et al., 2007) but application of gold clusters for treating in vivo or in vitro cancerous cell hyperthermia has not been developed yet under alternative magnetic force exposure which is a result of many factors such as redundancy in uncertainty of the mechanism, difficulty in technical procedure and of course minuscule specific absorption rate (SAR) compared to available magnetic nanoparticles.

6. Toxicity and safety consideration

In general, gold nanoparticles are well known non-toxic nanomaterials. However, they are divisive in vivo or in vitro reports about the gold nanomaterial toxicity in the literature. Surface chemistry, charge, shape and size of gold nanoparticles must be considered for biomedical application (Amini et al., 2017). Besides efficiency and technical challenges of different types of hyperthermia application of gold nanoparticles, gold nanostructures aren't biodegradable. Therefore, the nanotoxicity considerations are vague and contemplative (Fadeel and Garcia-Bennett, 2010; Amini et al., 2014; Amiri et al., 2018) and gold nanoparticles clearance is restricted by many limitations. Intrinsically, NIR mediated photothermal therapy requires bigger nanostructures in comparison with the type of gold nanoparticles that applicable for electric field or magnetic field hyperthermia that inclined to use smaller thiol-capped clusters. Mucociliary and hepato-biliary clearance is dominant for 18 nm PEGylated gold nanoparticles clearance compared to 1.8 gold nanoclusters that typically eliminated from renal clearance pathway (Lipka et al., 2010). Besides size and surface chemistry, the surface charge is affecting nanoparticles biodistribution and clearance. Compared to negatively charged thioglycolic acid-coated gold nanoparticles, intravenous injection of 2.8 nm positively charged cysteine coated gold nanoparticles resulted in the completion of different biodistribution and clearance profile in female Wistar-Kyoto rats (Hirn et al., 2011).

7. Conclusion

Except for photothermal therapy which has been evaluated in

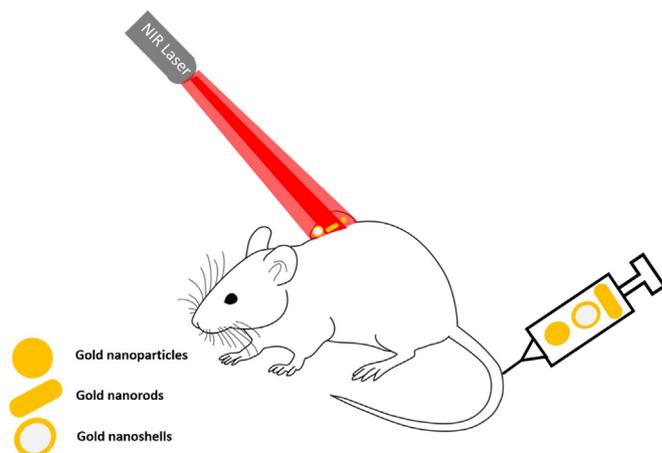


Fig. 2. Schematic view of in-vivo gold nanostructures mediated plasmonic photothermal therapy.

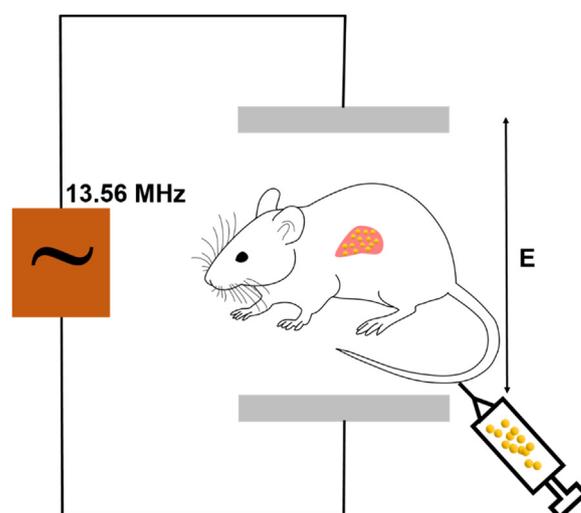


Fig. 3. Schematic view of in-vivo radio frequency electric field mediated thermal therapy by gold Nano clusters.

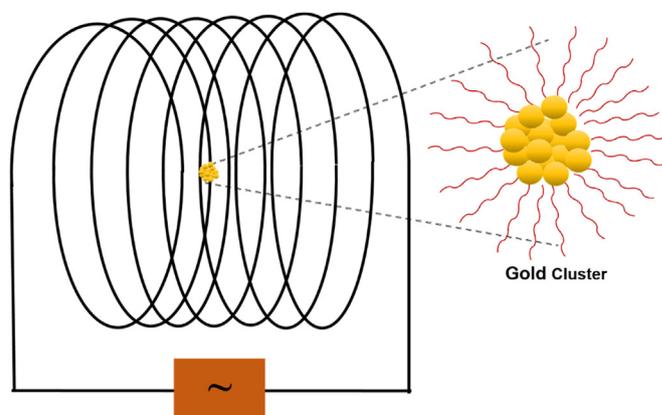


Fig. 4. Schematic view of gold Nano clusters heating under magnetic field exposures.

clinical trials, other techniques are under consideration in the early stages and don't acquire necessary scientific facts. However, unlike NIR radiation, Electric field, Magnetic field and Ultrasound exposure can reach to any point of the body. While there is a low likelihood that the researchers apply gold Nano cluster mediated hyperthermia in the

magnetic field due to the low amount of SAR. In contrary, the other two techniques proved promising results for heat generation of exposed gold nanoparticles. Figs. 1–4

Acknowledgments

This work was supported under grant number 96-03-223-31901 from Iran University of Medical Sciences (IUMS). Also, the author is thankful to S. H Mostafavi from the University of California Riverside for critical reading of the manuscript.

Declaration of interest

There is no conflict of interest to be declared.

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