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Laser-induced explosion of gold nanoparticles: potential role for nanophotothermolysis of cancer

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Aims: This article explores the laser-induced explosion of absorbing nanoparticles in selective nanophotothermolysis of cancer. **Methods:** This is realized through fast overheating of a strongly absorbing target during the time of a short laser pulse when the influence of heat diffusion is minimal. **Results:** On the basis of simple energy balance, it is found that the threshold laser fluence for thermal explosion of different gold nanoparticles is in the range of 25–40 mJ/cm^2. **Conclusion:** Explosion of nanoparticles may be accompanied by optical plasma, generation of shock waves with supersonic expansion and particle fragmentation with fragments of high kinetic energy, all of which can contribute to the killing of cancer cells.

Keywords: cancer therapy, gold nanoparticles, laser, thermal effects, thermal explosion

Nanophotothermolysis with pulsed lasers and absorbing nanoparticles (e.g., gold nanospheres, nanorods or carbon nanotubes) attached to specific targets has recently demonstrated great potential for selective damage to cancer cells [1–8], bacteria [3,6,9–11], viruses [6,11–14] and DNA [6,11]. When nanoparticles are irradiated by short laser pulses, their temperature rises very quickly to possibly reach thresholds for nonlinear effects (e.g., microbubble formation, acoustic and shock wave generation) leading to irreparable target (e.g., abnormal cell) damage. By engineering the laser wavelength, pulse duration and particle size and shape, this technology can provide highly localized damage in a controlled manner, potentially varying from a few nanometers (e.g., in DNA with a femtosecond laser) to tens of microns (the scale of single cancer cells) without damaging the surrounding healthy tissue. Among different nanostructures, gold nanoparticles (GNs) in different modifications (e.g., spherical, rods and shells) are the most promising candidates for photothermal (PT) sensitizers since they are strong absorbers, photostable, nontoxic, easily conjugated to antibodies (Abs) or proteins and have adjustable optical properties [15–20]. It has been discovered [2,3] that an accumulation of GNs on a cell membrane and, especially, formation of GN clusters (GNCs) leads to dramatic increases in bubble formation efficiency, resulting in more severe cancer cell damage at relatively low laser fluences of 60–80 mJ/cm^2, which is safe for normal tissues [4,21]. More effective bubble formation in a GNC is associated with optical [8] and thermal [4] amplification effects and, especially, with overlapping nanobubbles from a single GN as separate nucleation centers or the generation of one large bubble around a GNC as a single nucleation center due to rapid heat redistribution between very closely located GNs within a GNC [4,5]. Several methods to create GNCs with appropriate properties have been suggested and realized, including [6]:

- Targeting to the natural clustered cancer markers [4];
- Special engineering, such as a seprase human breast carcinoma MDA-MB-231 marker [4,5];
- Clustering secondary monoclonal Abs, such as IgG, conjugated with a GN around a single primary monoclonal Ab (e.g., F19) targeting individual cancer markers on a cell surface [4,5,9];
- Clustering viruses with an incorporated GN ('bio-GNC' as selective vehicles) into cancer cells [6,12,13];
- Concentrating GNs within vesicles during endocytotic internalization [2–5];
- Laser-induced GN aggregation [4];
- Using silver and gold kits to enhance GNCs [4].

After the pioneering demonstration of a new technology [1–3] and its further development [4–6], biomedical applications of pulse lasers with absorbing GNs and GNCs have become an extensive area of theoretical and experimental studies, as is shown elsewhere [22–28]. However, there is still a lack of detailed discussion of the mechanisms other than bubble formation around an overheated hot GN in a liquid environment, although it is very important for many application to determine when the threshold for bubble formation is high. In particular,

this situation is typical for precise DNA nanosurgery using small GNs (<10 nm) with very low efficiency of bubble formation [1,2], or for PT therapy of dense solid tumor, bones, atherosclerotic plaques and other targets with a lack of a sufficient amount of liquid for efficient bubble generation. However, during our studies, we have observed, besides bubbles, many other effects as signs of very high GN temperature, including:

- Appearance of yellow spots around cells with GNs owing to condensation of gold atoms [2,3];
- GNs melting with formation of gold craters caused by bubble interaction with gold liquid drops [4,6];
- Decrease of the sizes of GNs and their fragmentation [3];
- Disappearance of bubbles after the pulse with relatively high laser fluence (>0.5 J/cm^2) owing to GN disintegration [2,3];
- An increase in the efficiency of bubble formation after the pulse with relatively low laser fluence (≤0.1 J/cm^2) due to fusion of GNs or condensation of atoms on the parent GN (laser-induced GN aggregation effects) [4].

Building on these findings, we have proposed a new killing mechanism based on laser-activated 'gold atom bullets' that move from the explosion zone with kinetic energy that is sufficient to mechanically damage the surrounding cellular structures (this mechanism does not require a liquid environment) [2]. We have also discovered another new mechanism of PT nanotherapy, where a hot GN, especially a GNC, locally melts the surrounding dense structure, such as a bacterial wall, followed by GNC sinking into the wall, accompanied by destruction of the wall [3,6,9].

At the same time, the interaction of intense laser pulses with GNs, leading to the formation of spherical GNs (due to thermal ablation), GN size reduction, GN shape modification and similar effects, has been the subject of many independent studies [29–39]. However, these studies were performed without direct connection to biological applications. The main goal of this paper is to analyze the role of PT-based effects, besides bubble formation, around overheated GNs in cell damage, with a focus on thermal explosion. The obtained theoretical estimations are compared with our previous experimental results and the relevant data available from the literature.

Methods & design

Concept of selective nanophotothermolysis using laser-induced explosion of GNs

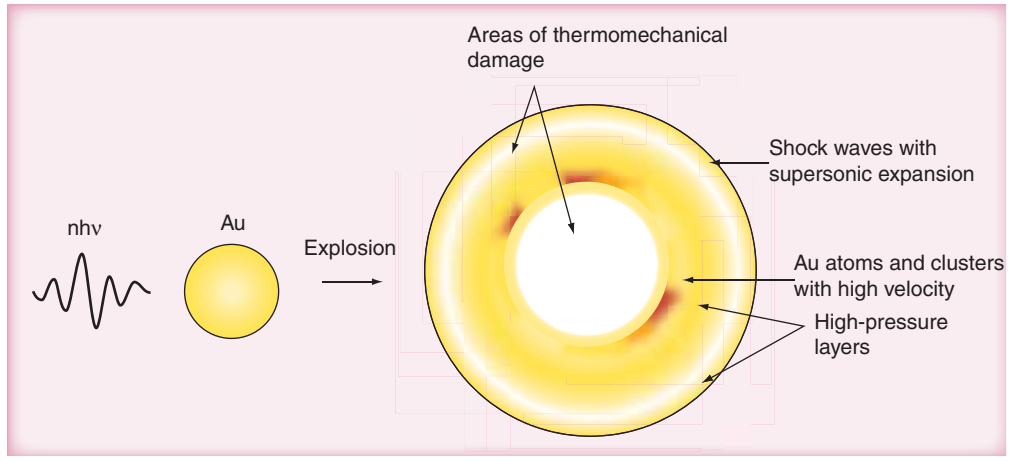
This concept is based on the recent significant extension of the theory of selective photothermolysis [40] for multiple absorbing nanotargets and their nanoclusters [4]. Here, one uses relatively small GNs (e.g., 10–40 nm in size) that can be selectively delivered to the targets (e.g., cancer cells) using different methods, such as physiological transportation, conjugation with antibodies and viruses and many others [1,3–6,9,12,14–19]. After GN delivery, these targets with selectively attached GNs are irradiated with short laser pulses. Sufficient energy transfer from the laser pulses with a specific laser fluence threshold (E_{expl}) to these GNs results in their explosion. Laser-induced rapid explosive evaporation of gold atoms and their clusters from GNs enables the generation of stress transients, shock waves and high local pressure. The extreme temperature rise can also induce explosive vaporization of a thin layer of fluid in contact with the particle, creating a conventional vapor bubble that expands rapidly on the nanosecond timescale [5], as the initial high vapor pressure overcomes the surface tension of the fluid. The expansion and, especially, collapse of bubbles can also cause a sound shock wave that travels outward and interacts with the cell, disrupting the cellular membrane. A phenomenological picture of these complex physical effects is shown schematically in Figure 1.

There are two main physical mechanisms that could lead to the laser-induced explosion of GNs – thermal explosion mode through electron–phonon excitation–relaxation and Coulomb explosion mode through multiphoton ionization.

Thermal explosion mode

Under the action of short laser pulses in the spectral range of the surface plasmon resonances (for a solid spherical GN the maximum absorption is ~520 nm), GN atoms are excited to upper electronic states owing to absorption of many photons. Through rapid (picosecond time scale) relaxation, GN atoms decay to their ground state with effective electron–phonon conversion of the absorbed photon energy into thermal energy. Depending on the GN temperature, T, the following effects alone or in combination can occur:

Figure 1. Laser-induced thermal explosion of a gold nanoparticle.



- $T < T_{LV}$, where T_{LV} is the liquid vaporization temperature (water in many cases), ~150–350°C [4–6,25,41]. This is thermal expansion of a single GN and surrounding thin liquid layer, which is accompanied by the generation of linear acoustic waves known as the 'classic' photoacoustic (PA) effect;
- $T_{LV} \leq T < T_{GNM}$, where T_{GNM} is the GN melting point, ~1063°C [29]. This is bubble formation with expansion and collapse, which is accompanied by the production of acoustic and shock waves [40–43];
- $T_{GNM} \leq T < T_{GNB}$, where T_{GNB} is the GN boiling point of ~2710°C [29], with GN melting;
- $T \geq T_{GNB}$, which is GN boiling with the formation of gold vapor around liquid gold drops.

The PT process (step 3), and especially step 4, may lead to GN fragmentation into smaller parts and to the thermal explosion of a GN into single atoms.

Coulomb explosion mode

For ultrashort laser pulses (e.g., femtosecond time scale), comparable to the time scale of electron–electron interactions and shorter than the electron–phonon interaction time, a non-PT mechanism of GN explosion can occur through multiphoton ionization, when absorbed photon energy is transferred directly to the electrons, leading to their ejection due to the Coulomb explosion mechanism [33,37]. High GN plasmon-resonance absorption may facilitate this effect due to thermionic electron emission. An analysis of the Coulomb explosion mechanism is outside the topic of this article.

Cell damage effects

The therapeutic effect of laser-induced explosion of GNs for cancer treatment can be reached owing to one or several phenomena, such as protein inactivation (e.g., through its denaturation or coagulation) around hot GNs [24], bubble formation [1–5], generation of acoustic and shock waves [41–44] and interaction with GN fragments and atoms [2]. An important damage-related factor is not only the temperature but the vapor pressure produced by both water and gold vapors, accompanied by the cavitations and shock waves, with local pressure up to gigapascals [42–44]. The damage to specific cellular structures (e.g,. plasmatic membranes, nuclei, cytoskeletons or organelles) in the laser explosion mode depends on GN parameters (composition, size and shape), their number and location, laser parameters (wavelength, fluence, pulse duration and number of pulses) and properties of the surrounding media (e.g., amount of water).

Time-scale approximations

The goal of the theoretical modeling is to estimate the threshold laser energy density, E_{expl}, required for realization of the thermal explosion mode of GNs and to compare the calculated data with available experimental results. This mode is realized through the rapid overheating of a strongly absorbing target during a short laser pulse when the influence of heat diffusion is minimal. Let us first estimate the time scale for thermal relaxation due to heat diffusion from the surface of the nanoparticle.

In the vicinity of GN $\leq 5R$, where R is the nanoparticle's radius, the thermal relaxation time for a spherical GN can be estimated as

$\tau_T = R^2/6.75k$, where k is the thermal diffusivity [4]. For R = 50, 100 and 200 nm, estimates of τ_T (for water, $k = 1.44 \times 10^{-3}$ cm^2/s) are approximately 2.6, 10 and 41 ns, respectively. For a laser pulse duration $t_P \leq \tau_T$, heat is generated within the GN more rapidly than can be diffused away, thus we can neglect heat losses from the surface of the GN due to heat diffusion into the surrounding medium. This condition for smaller GNs is valid with picosecond and femtosecond laser pulses. However, we consider here nanosecond pulse durations because most of the experimental results (ours and others) have been obtained with lasers generally used in the biomedical field (t_P ~5–12 ns), which are less expensive and less harmful to normal tissue (compared with picosecond and femtosecond lasers [4]) and still satisfy the condition $t_P \leq \tau_T$ for relatively large GNs. With this assumption, the probability of a non-PT mechanism of explosion is very low because multiphoton ionization usually occurs more effectively under supershort femtosecond pulses [37].

Threshold intensity for laser-induced thermal explosion

Consider a nanoparticle delivered selectively to a targeted site (e.g., cancer cell) to be irradiated by a laser of intensity I. The power of the absorbed electromagnetic field is $P = \sigma_{abs} I$, where σ_{abs} is the GN's cross-section of absorption. If σ_{abs} is large enough, thermal explosion of the GN may occur at certain values of the threshold laser intensity I_{expl}, which is less than the threshold intensity for optical plasma formation in the surrounding medium [45]. Under the thermal explosion of GNs, we can understand the specific case for which the total energy absorbed by the GN during the time of its inertial retention in vapor state, $\tau_{expl} = R/u_s$, exceeds the energy required for the GN's complete evaporation, $\rho qV = N_{Au} q_1 V$. Here, u_s is the sound velocity in Au vapor at the critical temperature $T_{cr} \sim T_{GNB}$; ρ is the volume density of GN; N_{Au} is the number of Au atoms per unit volume; q and q_1 are the particle's specific heat of evaporation per unit mass and per particle, respectively; and V is the GN's volume. We have a laser pulse duration of τ_L (~10 ns) >> $\tau_{expl} = R/u_s$ (~1 ps for R ~10 nm), where τ_{expl} is an explosive evaporation time.

To compute I_{expl}, we can write the following energy balance equation:

$$\sigma_{abs} I_{expl} \frac{R}{u_s} \approx \rho q V$$

In terms of the absorption efficiency,

$$K_{abs} = \frac{\sigma_{abs}}{\pi R^2}$$

the threshold intensity of the laser radiation for thermal explosion of the spherical GN can be expressed as:

$$I_{expl}(R) \approx \frac{4\rho q u_s}{3K_{abs}(R)}$$

Thus, the solid nanoparticle in a relatively strong laser field with intensity $I \geq I_{expl}$ during the short time $\tau_{expl} \sim R/u_s$ transforms into a gas (vapor) sphere of radius ~R, which has high temperature $T \sim T_{GNB}$ and high pressure $P_{vap} >> P_\infty$, where P_∞ is the ambient pressure.

We assume here that a thermal explosion of a GN is accompanied by the generation of shock waves that expand with a supersonic velocity

$$u_s = \frac{R}{\tau_{expl}} = \frac{I_{expl}}{4\Delta H} \approx 10^5 cms^{-1}$$

Here, $\Delta H = \Delta H_{300\text{-}vap} + \Delta H_{vap}$, where $\Delta H_{300\text{-}vap}$ is the enthalpy change per unit volume for heating the GN from the ambient temperature to the vaporization temperature and ΔH_{vap} is the vaporization enthalpy per unit volume. The shock waves could be waves of high acoustic and/or water vapor pressure, which spread out over long distances around an epicenter of explosion and produce irreparable mechanical cell damage [42,44]. It should be noted that the pressure produced by vaporization of a GN itself (e.g., ~10^{-2} atm [37]) is less than water vapor pressure around the hot GNs [37,42]. Indeed, the number of atoms vaporized per unit of time and per unit of particle surface is given by [46]:

$$\frac{N_{vap}}{dt} = u_s N_{Au} = \frac{I_{expl}}{4\Delta H} N_{Au}$$

For example, the atomic density of bulk gold is 5.9×10^{22} cm^{-3}, while each GN contains approximately 10^9 atoms, leading to an average atom density of 10^{17} cm^{-3}. Higher gold vapor pressure can only be reached on the front of the explosion, where explosion products are localized in a thin layer.

Results & discussion

The cell and biological tissue damage and killing effects produced by the shock waves have been studied experimentally and theoretically during the past 10 years [47–52]. The time required to destroy an abnormal cell of size d by

supersonic expansion of shock waves can be roughly estimated as $\tau_{sw} \approx d/u_s$. In the case of 15-μm diameter cancer cells [5], this time is $\tau_{sw} \approx 15$ ns, which is comparable with the lifetime of sound/pressure shock waves in an aqueous medium. We can estimate the lower level of the threshold energy density of a laser pulse required for thermal explosion of the GN using:

$$E_{\exp l}(R) \approx I_{\exp l}(R) \times \tau_{\exp l}$$

where the threshold intensity, I_{expl}, depends on the absorption efficiency of the nanoparticle. For the particular laser used in the experiments [5] (λ = 532 nm, τ_L = 8–10 ns), the threshold energy density for thermal explosion of a solid gold nanosphere of size R = 35 nm (absorption efficiency of K_{abs} = 4.02 [5]) is E_{expl} = 38.5 mJ/cm^2. The laser threshold energy density, E_{expl}, strongly depends on the types of nanoparticles (e.g., gold solid nanospheres, nanoshells and nanorods) [7,8,15–17]. For example, gold nanorods have a near-IR resonance absorption efficiency of approximately 14 for an effective radius of 11.43 nm [26]. Owing to the higher plasmon-resonance absorption efficiency of nanorods, the threshold energy density can be reduced by using gold nanorods up to E_{expl} = 25 mJ/cm^2. It is important to note that the estimated threshold energy densities for the thermal explosion of GNs at the given wavelength λ = 532 nm are almost 2.5–4-times less than the laser fluence of 100 mJ/cm^2 established as the safety standard for medical lasers [21].

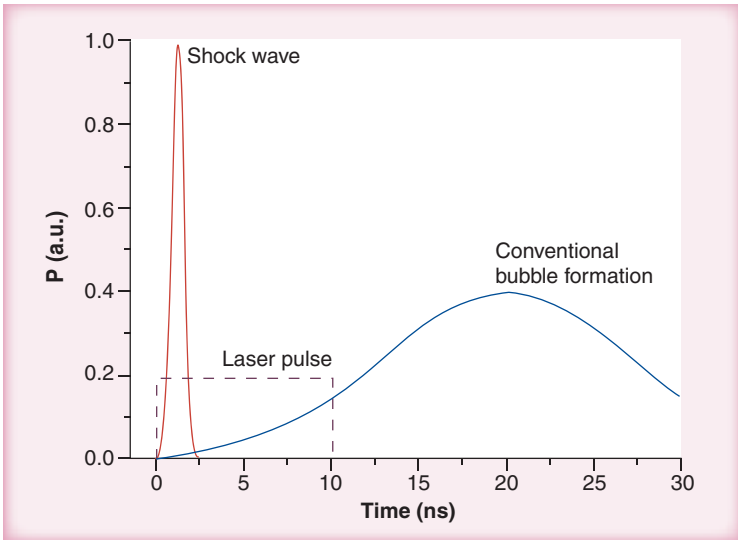
The estimated values for E_{expl} are in agreement with some available experimental results. Indeed, for spherical GNs with an average size of 45 nm irradiated with second-harmonic Nd:YAG laser pulses (532 nm for 7 ns), the laser fluence threshold for changing the GN shape and its fragmentation associated with GN melting and boiling phenomena are 16 and 30 mJ/cm^2, respectively [29]. The more intense GN fragmentation to small fragments of mainly 5–10 nm in size has been observed for laser fluences in the range of 30–140 mJ/cm^2 and higher [29]. For a 30-ps pulse, 25-nm GN fragmentation has been observed at 23 mJ/cm^2, with a slight effect on changing the GN shape, even at 2–5 mJ/cm^2 [34,35].

The thermal explosion effect can explain our experimental observation of a yellow spot on a slide with cancer cells labeled with 40-nm GNs for laser fluences of 60–100 mJ/cm^2 [2,4] and fragments of GNs and GNCs (with 40 nm GNs) with sizes 100–300 nm under similar laser fluences [4]. It is important that the radius of yellow spots exceeds the size of the cells, indicating a high initial kinetic energy of gold atoms and their clusters during thermal explosion, which is crucial to the damage of cell membranes. According to the experimental findings, complete damage of breast cancer cells in suspension *in vitro* with 40-nm GN is approximately 60–80 mJ/cm^2 at a wavelength of 532 nm with no harmful effects on healthy cells [2,4,7]. We have also determined *in vivo* with mice that, in the near-IR range (window transparency of most biotissues), the damage threshold for cancer cells (human squamous carcinoma) labeled with gold nanorods with maximum absorption at wavelength 840 nm is approximatley 58 mJ/cm^2 [7].

Thus, thermal explosion around GNs may give a significant contribution to cell damage alone or together with conventional water vapor bubble formation in nanophotothermolysis, which is characterized by a higher laser fluence range of 50–500 mJ/cm^2 [1–5,22–25,27–30]. As mentioned previously, conventional bubble formation usually starts at the end of the nanosecond laser pulse [4,5,41], while the thermal explosion time scale is from a few picoseconds to a few nanoseconds [30–32]. A schematic time scale for shock wave and conventional bubble formation in thermal explosion mode is shown in Figure 2. Thus, shock waves appear earlier than bubbles induced by the explosive vaporization of GNs in a liquid environment.

With a decrease in GN size comes an increase in the temperature as ~1/R (the absorbed energy is proportional to the cross-section of GN divided by the GN volume) at the same laser energy level, while the efficiency of water bubble formation drops as ~1/R [1,4]. Besides, the melting point of GN significantly decreases when the particle diameter is less than 5 nm [38]. Thus, more effective heating and hence realization of thermal explosion is expected for small GNs, given the low efficiency of conventional bubble formation associated with liquid thermal evaporation. For example, a thermal explosion should participate in the formation of nanobubbles on the scale of 20 nm with subnanosecond duration around GNs of size 9 nm irradiated with femtosecond pulses (100 fs, 290 mJ/cm^2) [30]. The thermal explosion mode can also explain our observations of partial damage of K-562 cells, even with GNs of size 5–10 nm, irradiated with nanosecond pulses (8 ns, 100–500 mJ/cm^2) when heat diffusion significantly inhibits the conventional mechanism related to water bubble formation [2,3]. According to our findings, the most effective cell killing occurs when GNs are

Figure 2. Schematic time scale for shock wave and conventional bubble formation using the thermal explosion mode.



located on or (especially) inside a cell membrane to provide membrane rupture, even with a single GN or a GNC consisting of just few GNs (~3–5) [2,4].

The laser-induced explosion effect can explain another of our results with notable cancer damage with 1.4 nm GNs inside viruses on a cell membrane with picosecond laser pulses (30 ps, 50–100 mJ/cm^2) when the probability of classic water bubble formation is very low [6]. We believe that the explosion mode may be essential in selective nanophotothermolysis of DNA [11] and this mode is definitely becoming dominant in the absence of a sufficient amount of water around the GNs. This mode can be combined with a recently proposed bubble-overlapping mode [5], where the explosion of a few closely located GNs in a GNC can produce one large bubble with enhanced killing efficiency. The explosion of GNs on smaller particles or a single gold atom during a laser pulse may provide the condition for the interaction of the pulse with its atoms, leading to their ionization and plasma formation. However, these effects should appear at relatively high laser fluences (~1 J/cm^2 and greater) that are not safe for normal cells [21].

Conclusion

We have considered a new mechanism for selective laser killing of abnormal cells by laser thermal explosion of single nanoparticles (nano-bombs) delivered to the cells. Thermal explosion is realized when heat is generated within a strongly absorbing target more rapidly than the heat can diffuse away. On the basis of simple energy balance, it is shown that the threshold energy density of a single laser pulse required for the thermal explosion of a solid gold nanosphere is approximately 40 mJ/cm^2. The nanoparticle's explosion threshold energy density can be reduced further (up to 11 mJ/cm^2) by using relatively large nanorods (and probably nanoshells) and many other advanced GNs whose optical plasmon resonance lies in the near-IR region, where the biological tissue transmissivity is the highest [16,17]. Additionally, the effective therapeutic effect for cancer cell killing is achieved owing to nonlinear phenomena that accompany the thermal explosion of the nanoparticles, such as the generation of GN explosion products with high kinetic energy as well as strong shock waves with supersonic expansion in the cell volume or producing optical plasma. It is important that most of these phenomena can explain some published experimental results whose interpretation was performed without taking into account this effect.

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