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Investigation of energy absorption by clustered gold nanoparticles

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ABSTRACT

The utilization of gold nanoparticles (GNPs) as a radiation sensitizer has received broad attention. Although GNPs form clusters in living cells, most previous simulation studies have assumed a homogeneous distribution of GNPs. In this study, a GNP cluster was constructed for simulations and the impact of cluster formation on dose enhancement was examined. Energy absorption by the GNPs was compared between clustered and homogeneous distributions for several different GNP concentrations and diameters under 100 keV X-ray irradiations. Our simulations showed that clusters more efficiently absorbed the secondary electrons and photons produced by GNPs themselves. Furthermore, the impact of cluster formation on dose enhancement was more significant for smaller GNPs and higher concentrations. Our results suggest that previous simulations assuming a homogeneous GNP distribution have overestimated the dose enhancement, especially for smaller GNPs and higher concentrations. These findings should guide the selection of GNP size and concentration for effectively optimizing dose enhancement in future studies.

1. Introduction

The past twenty years have seen increasingly rapid advances in the field of nanotechnology in medicine. In particular, gold nanoparticles (GNPs) have especially attracted attention as a radiation sensitizer, principally due to three advantageous properties: easy surface functionalization; high biocompatibility; and high atomic number (Z = 79). GNPs are preferentially taken up in tumor cells when conjugated to peptides [1], antibodies [2] or polyethylene glycol (PEG) [3,4]. GNPs inside cells physically interact with therapeutic radiation and emit electrons, which cause local dose enhancement. These electrons or generated reactive oxygen species (ROS) damage critical structures such as DNA or mitochondria, leading to radiation sensitization [5–8]. Many groups have experimentally observed an increase of DNA double strand break yields in cells which contain GNPs under kV and MV X-ray irradiation [9–11]. Chithrani *et al* have investigated GNP size dependency on cell survival fraction [12]. An *in vivo* study performed by Hainfeld *et al* reported radiation sensitization and tumor regression with 1.9 nm diameter GNPs under 250 kVp X-ray irradiation [13].

The dose enhancement induced by GNPs has been estimated using Monte Carlo simulations. Several studies have reported higher dose enhancement under lower energy X-ray irradiation since the dose enhancement is caused mainly by photoelectric and Auger electrons [14–17]. To date, several simulations have been carried out under the assumption that GNPs are homogeneously distributed inside the tumor cells [18–22]. However, previous *in vitro* experiments showed that GNPs actually form clusters [11,23–26]. When GNPs form clusters, the separation of GNPs becomes significantly smaller than that in homogeneous distributions and this closeness is expected to cause increased electron absorption by the surrounding (“bystander”) GNPs. In other words, clustered GNPs would be expected to show lower dose enhancement than non-clustered GNPs. Recently, Zygmanski *et al* simulated the dose enhancement in simple planar array and slab cluster models and showed saturation of dose enhancement as the number of

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GNPs in the cluster increased [27]. Planar or hexagonally packed GNP clusters were previously investigated by other groups [28,29]. On the other hand, quantitative image analysis suggested that GNPs in clusters can actually become trapped inside vesicles [24]. By using parameters given by Peckys and De Jonge, Jeynes *et al* calculated the number of secondary electrons exiting the GNPs [30]. However, the direct cause of lower dose enhancement in clusters is the increased energy absorption by the surrounding GNPs instead of the surrounding water medium and the extent of this effect remains to be fully elucidated. We hypothesize that the energy absorption by the surrounding GNPs should be highly influenced by the inter-GNP separation in clusters.

Therefore, the objective of the present study is to evaluate the radiation absorption by clustered GNPs with use of a realistic model that enables us to investigate the effect of inter-GNP separation. We assess the impact of GNP size and concentration as determining factors of the GNP separation on energy absorption. Firstly, in a macroscopic study, we constructed a GNP cluster model using parameters reported previously [24] and compared the energy absorption between clustered and non-clustered GNPs. Then, we conducted a microscopic study with a simple two GNP model to better understand the energy absorption by the bystander GNPs as a function of GNP separation.

2. Materials and methods

2.1. General

Macroscopic and microscopic studies were performed using, Geant4 (version 10.02.p02) Monte Carlo simulation code [31,32]. Low energy electromagnetic physics list “Geant4-Penelope” was used to track low energy electrons. Energy cutoff lengths were 1 nm for all particles and the production threshold of secondary electrons was set to 250 eV. Atomic de-excitation processes, fluorescence emission, Auger electron emission, Auger cascade, and Particle Induced X-ray Emission (PIXE) were all activated. Monochromatic 100 keV X-rays were chosen as the source radiation, because bombardment of polychromatic X-ray complicates analysis of the pure energy absorption phenomenon, especially in microscopic studies. The number of incident particles was 4.8×10^9 and 10^8 for macroscopic and microscopic studies, respectively.

2.2. Macroscopic study

GNP distributions were simulated inside a cubic cell phantom filled with water, referring to the report by Peckys and De Jonge [24], in which quantitative measurements of cluster formation in living COS-7 cells were performed. Energy deposition to the whole volume of water medium and GNPs by physical interaction with X-rays is referred to as “energy absorption”, and was compared between clustered and non-clustered GNP distributions. Hereafter, these two types of spatial distributions are referred to as “Cluster” and “Homogeneous”.

The volume of the COS-7 cell line used by Peckys and De Jonge was not reported [24]. Therefore, we derived the average volume from the BioNumbers website as 2016 μm^3 [33]. Each side of the cubic cell phantom was accordingly set to 12.6 μm. For Homogeneous simulations, spherical GNPs were randomly distributed within the cell phantom (Fig. 1(a)). In contrast, for Cluster simulations, GNPs were placed inside a cluster sphere positioned at the center of the cell phantom (Fig. 1(b)). The diameter of the cluster sphere was 4.6 μm. One hundred and sixty four spherical vesicles of 260 nm diameter were randomly distributed inside the cluster sphere and GNPs were randomly distributed within each vesicle (Fig. 1(c)). Three diameters of GNPs (10, 30 and 50 nm) were compared to evaluate GNP size dependency on energy absorption. The weight concentration of GNPs was set to 0.5, 1, 2 or 3 mg/mL for both the Cluster and Homogeneous simulations, enforcing a consistent number of GNPs in both cases. Table 1 summarizes the number of GNPs in the cell phantom and vesicle for each case. This specification of cluster geometry allows us to investigate the separation between GNPs for each diameter and weight concentration.

Monochromatic 100 keV X-rays were shot in parallel from one side of the cell phantom. Although this energy is relatively low compared to the energy usually used in clinical examinations, it is relevant because therapeutic X-rays scatter deep inside the body [34], and the energy is higher than the K-shell energy of gold (80.7 keV).

The influence of clustering was evaluated for GNPs with the same weight concentration and diameter by the Clustering Factor. Clustering Factor is given by the ratio of energy absorption by GNPs between Cluster and Homogeneous (non-clustered) distributions, as follows:

$$Clustering\ Factor = \frac{Energy\ absorbed\ by\ clustered\ GNPs}{Energy\ absorbed\ by\ non\text{-}clustered\ GNPs} \quad (1)$$

Thus, by definition, this factor will increase if additional energy absorption is measured in Cluster compared with Homogeneous distributions. Next, to evaluate the fraction of energy absorbed by the GNPs compared with the whole cell phantom, the macroscopic Relative Energy Absorption (REA_{Macro}) was defined for both Cluster and Homogeneous GNP distributions. REA_{Macro} is given as the ratio of energy absorbed by GNPs to the total energy absorbed in the whole region of interest (*i.e.* all the water and GNPs inside the cubic cell phantom) as follows:

$$REA_{Macro}\,[\%] = \frac{Energy\ absorbed\ by\ GNPs}{Energy\ absorbed\ by\ water\ medium + Energy\ absorbed\ by\ GNPs} \times 100 \quad (2)$$

Note: Clustering factor (Eq. (1)) does not consider absorption by water.

2.3. Microscopic study

The main aim of the microscopic study was to gain a better understanding of the mechanisms behind the macroscopic behavior described above, by analyzing the energy absorption by bystander GNPs in a simple two-GNP geometry. Hereafter, the closest GNP from the source GNP of interest is referred to as “Bystander GNP”. Cylindrical GNPs were used here instead of spherical GNPs to clarify how the energy absorption changes as a function of inter-GNP separation; and hence, the distance from source GNP surface to the bystander GNP. The use of cylinders enables us to fix the distance between the flat base of the source GNP cylinder and the base of the bystander GNP to a constant value (if spheres were used, surface curvature would enforce a variable separation between GNPs). The utilization of cylindrical (rod-shaped) GNPs as a radiation sensitizer has already been extensively studied for both *in vitro* and *in vivo* studies [35,36].

A cylindrical GNP was first positioned at the center of the same cubic cell phantom used for the macroscopic simulations. 100 keV X-rays were incident on the GNP from a disc source, connected to the surface of the GNP and the same diameter as the GNP. The energy distributions of the electrons and secondary photons exiting the GNP were derived. Subsequently, these energy distributions were used as the source radiation; 10^8 particles were shot at another (bystander) GNP, positioned along the central axis of the cylinder, 0 to 500 nm away from the disk source located at the center of the cell phantom. At each separation, energy deposition to the surrounding water in the cell phantom and the energy absorption by the bystander GNP was calculated. The diameter and height of the GNPs was always the same as the diameter of the source and set to 10, 30 or 50 nm.

The energy absorption by the bystander GNP was evaluated by the microscopic Relative Energy Absorption (REA_{Micro}), defined similarly to the REA_{Macro} (Eq. (2)).