Radiobiological modelling of clustered gold nanoparticles with different treatment time

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1. Introduction

Gold nanoparticles (GNPs) have been shown to greatly increase the efficacy of radiation [1]. Low-energy photons have high interaction probability with gold. Generated substantial number of secondary electrons deposits highly localized dose near the GNPs.

To describe cell survival with GNPs, high dose spikes around GNPs were simulated and used for development of GNP-local effect model (LEM). Previous researches simply assumed uniformly distributed individual GNPs at certain GNP-exposure time [2, 3]. However, we present radiobiological modelling depending on clustered behavior of GNPs and different GNP-exposure time observed by optical diffraction tomography (ODT).

2. Methods and Results

2.1 Imaging of gold nanoparticles

Three-dimensional localization of GNPs inside the human breast cancer cells (MDA-MB-231) was assessed using commercialized ODT setups (HT-1S, Tomocube, Inc., South Korea), which exploit refractive index (RI) as imaging contrast. The cells were treated with 500 μg/ml of 1.9 nm GNPs (Nanoprobes Inc., Yaphank, NY, United States) and incubated for 1, 2, 12, and 24 h.

To determine the RI values of GNPs, average RI histograms were compared between GNPs-treated and control cells. For RI values higher than 1.38, larger number of counts were observed with GNP-treated cells compared to control cells. Since it has been reported that the RI values of cell cytoplasm were within the range of 1.37- 1.39 [4, 5]. The regions with RI values higher than usual cytoplasm were assumed to correspond to GNPs.

Considerable number of GNPs clustered in cytoplasmic lysosomes and they were internalized into the cell in 1-2 h. Some of clustered GNPs were likely transported outside the cell through exocytosis and others remained in the cytoplasm as times evolved.

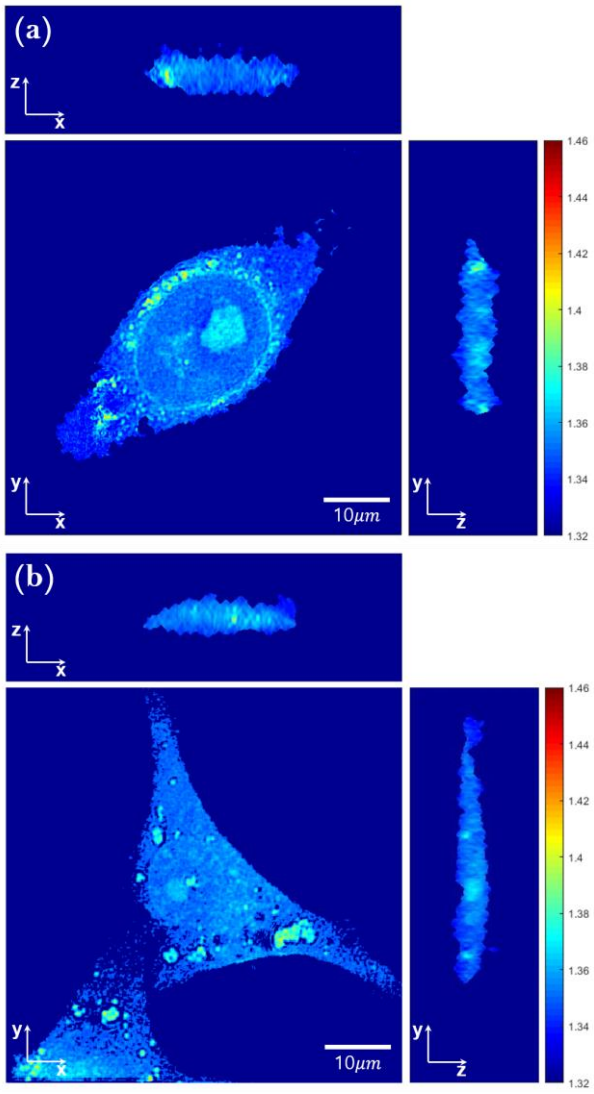

Fig. 1. Cross-sectional slices of the 3D RI tomogram of a MDA-MB-231 human breast cancer cell after (a) 1h and (b) 12h treatment of GNPs. The values on color bar are corresponding refractive indices.

2.2 Simulations and Modeling

Using Geant4-DNA, Monte Carlo simulations were carried out to calculate nanoscale dose near single GNP.

The GNP were irradiated with 150 kVp photons with 2 mm filter of X-RAD 320 spectrum (Precision X-Ray, North Branford, CT, United States). The major and minor diameter of MDA-MB-231 were assumed as 15.5 and 11.5 μm. Total 10^8 GNPs were distributed within a cell either individually or in the clustered forms. For clustered GNPs, they were assumed to be taken up inside vesicles with different number of GNPs per vesicle (Fig. 2(a) and (c)). Also, vesicle distributions were randomly selected either uniformly within the cytoplasm or using an exponentially decreasing likelihood with distance from the nucleus (Fig. 2 (b) and (d)). The dose distributions around the GNP were superimposed and cell survival was calculated based on developed GNP-Local Effect Model (LEM) [6]. The sensitizer enhancement ratio (SER) was defined dividing the area under the curve of non-exposed cells with GNP-exposed cells.

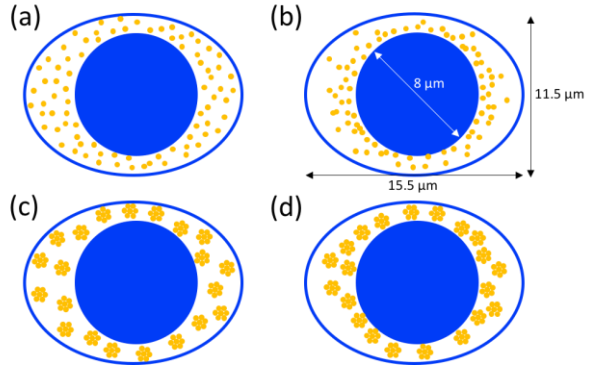

Fig. 2. Schematic diagram of GNPs distributions inside the cell. (a) uniformly and (b) exponentially distributed individual GNPs and (c) uniformly and (d) exponentially distributed clustered GNPs

Since radial dose around the GNP rapidly falls off as distance increases, sensitivity enhancement was increased up to 1.61 with exponentially distributed individual GNPs (μ=0.1). However, when each vesicle contains 10^3 GNPs, cell radiosensitization effects were slightly reduced with clustered GNPs.

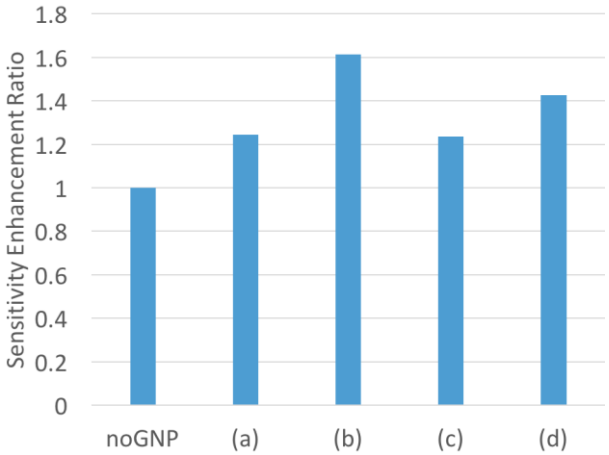

Fig. 3. Sensitivity enhancement ratio depending on distributions of GNPs. (a) uniformly and (b) exponentially distributed individual GNPs and (c) uniformly and (d) exponentially distributed clustered GNPs

3. Conclusions

Three-dimensional localization of clustered GNPs was assessed in the cells as times evolved using ODT. Based on GNP-LEM, radiosensitization effects were estimated with clustered GNPs distributions in the cytoplasm.

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