Quantitative Characterization of Free Radical Generation Under High-Energy Photon Irradiation for Gold Nanoparticle Mediated Radiation Therapy

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Introduction

Multiple *in vivo* and *in vitro* studies demonstrated that the biological effect of cell irradiation is greatly enhanced in the presence of gold nanoparticles (GNP). Since the associated physical dose enhancement is relatively small under high energy photon sources, we propose that the primary mechanism responsible for this tumoricidal effect is an increase in generation of reactive oxygen species (ROS) in aqueous media at the nanoparticle surface.

Measurement of the ROS generation is challenging due to a very short average life of those species. We have developed and validated a new approach to quantify them through fluorescence spectroscopy. A comparison of the ROS yield in water only and water with gold nanoparticles was done for a set of GNP concentrations. A Monte Carlo model of the experimental setup geometry was created in order to evaluate the increase in physical energy deposition in the presence of GNPs.

Methods and Materials

A solution containing 0.0005 mg/ml concentration GNPs (citrate coated, particle diameter 30nm) were mixed with anthracene derivative (Antheracene-9,10-dipropionic acid disodium salt) dissolved in dimethyl sulfoxide. Samples in glass capillaries were irradiated under Ir-192 HDR treatment source (average energy ~380keV). NaCl (concentration 1% w/v) was added to samples after irradiation in order to segregate nanoparticles at the bottom of capillaries. Fluorescence spectroscopy was performed on irradiated samples within several hours; the intensity of 430nm peak emitted by anthracene molecules was used to quantify the ROS generation.

Monte Carlo simulation of the experimental geometry was conducted using MCNP5 package. The used concentration of GNPs translated to 3.2×10^6 particles of 30 nm diameter uniformly distributed in a 1.2mm-side cubic aqueous volume. Average energy deposition values in the aqueous volume were scored with F8* tally, cut-off energies for both photons and electrons were set to 10keV. Simulations were run for 5×10^8 histories to achieve the relative error below 1%.

Results and Discussions

The anthracene derivative salt is a fluorescent molecule that selectively reacts with ROS. A larger amount of ROS will be produced in the aqueous media under higher irradiation dose levels, resulting in increased oxidation of the sensor molecule, in turn leading to depletion in the number of unoxidized sensor molecules in the solution. Thus reduced fluorescence signal from anthracene would be detected in presence of higher quantities of ROS in the sample.

We normalized the fluorescence signal intensity to that of 0 Gy for both GNP solution and pure water to compare the enhancement. The ROS yield, which is also the amount of reacted anthracene, is simply calculated as:

$$ROS\ yield = 1 - normalized\ fluorescence\ intensity$$

The ROS yield enhancement due to GNP is defined as:

$$Enhancement = \frac{ROS_{GNP} - ROS_{water}}{ROS_{water}} \times 100\%$$

The ROS yield and the corresponding enhancement vs irradiation dose are plotted in Figure 1 and Figure 2.

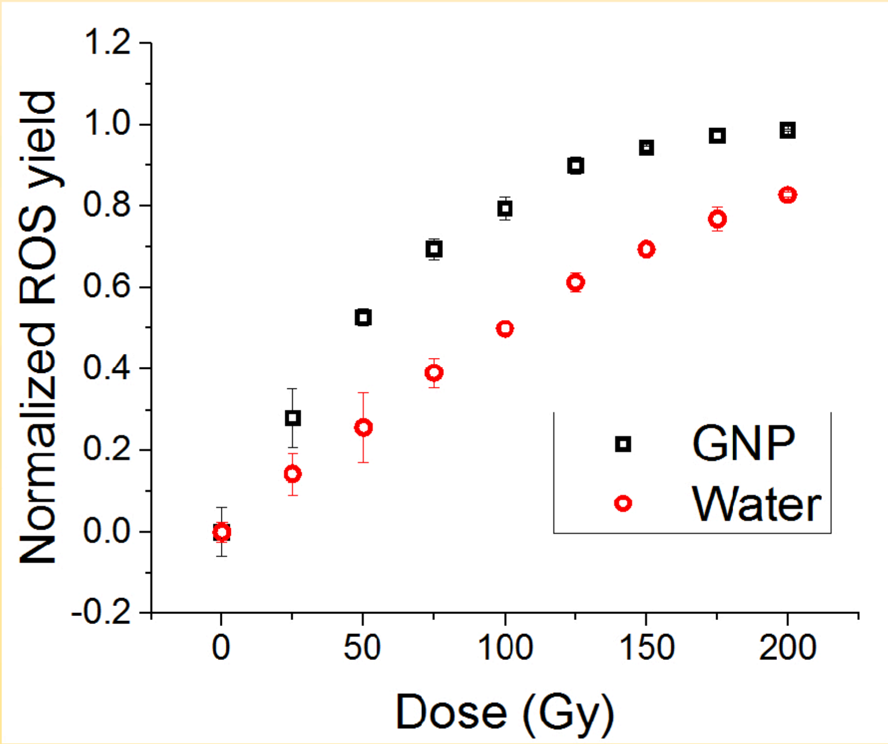

Fig.1 Normalized ROS Yield vs Dose

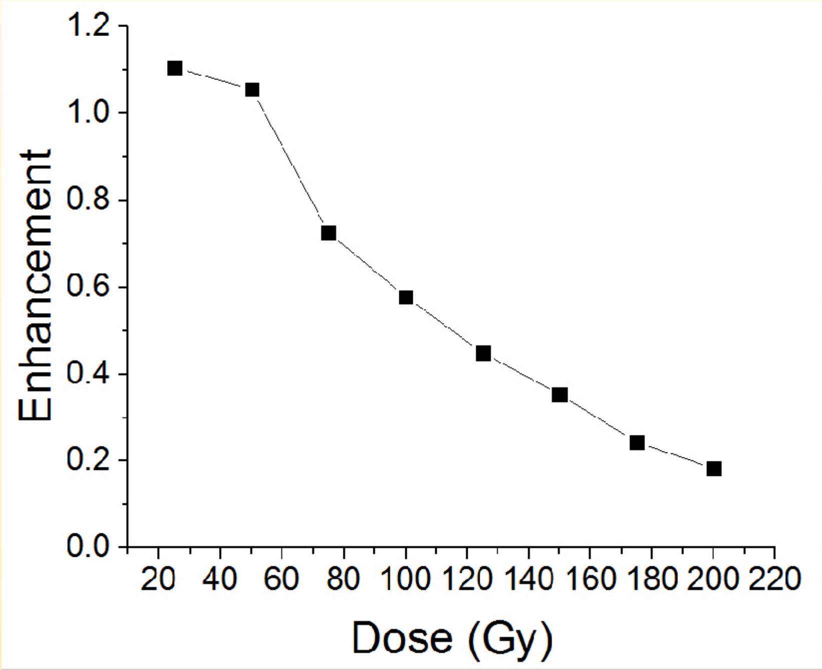

Fig.2 Enhancement vs Dose

dose range, showing saturation at higher doses, especially for GNP samples. The yield enhancement up to 110% in presence of GNP was observed around 25Gy radiation dose. The enhancement decreases as the dose increases, which can be attributed to quenching of ROS due to interaction with gold nanoparticles upon reaching a certain concentration .

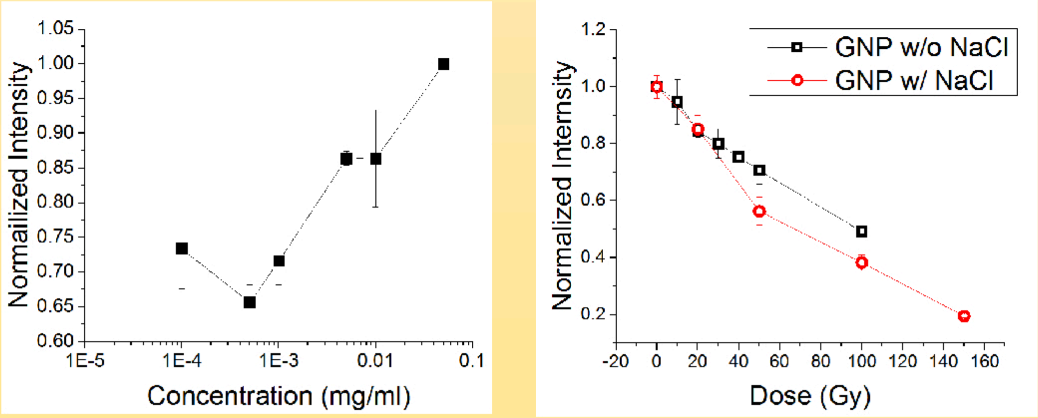

Fig.3 Normalized fluorescence intensities vs GNP concentration (Left); comparison of with and without NaCl (Right)

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The latter quenching effect was noticed during the initial experiment stage. We first tested several different GNP concentrations under same radiation dose level and found that 0.0005 mg/ml gives the best ROS yield, as shown in Fig. 3 (Left). We also tried some approaches to segregate the nanoparticles from the sample after irradiation, including adding NaCl salt to destroy the citrate coating, and centrifuge the samples to precipitate the nanoparticles. NaCl showed a clear positive effect on decreasing and stabilizing the fluorescent signal, as evident from Fig. 3 (Right), but centrifuge had no impact on the result. For both experiments in Fig. 3 the GNP concentration was 0.0005 mg/ml. NaCl concentration was 1% w/v, close to that of saline solution.

For the Monte Carlo simulations, we ran several trials with different random seed to average the output tallies. The result of energy deposition in GNP group shows a 1.5% higher than that of water group, with percentage error of 0.68%. This enhancement value in simulation is dose independent.

Conclusion

Free radial generation by water radiolysis can be quantitatively characterized by fluorescence spectroscopy. The experimental approach has been developed and validated. Dose enhancement in aqueous media due to the presence of gold nanoparticles is vastly dominated by ROS production increase, mediating the biological response to high-energy photon irradiation.

References

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