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Mitochondria as a target for radiosensitisation by gold nanoparticles

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Abstract. While Gold Nanoparticles (GNPs) have been extensively studied as radiosensitisers in recent years, there is a lack of studies of their impact on targets outside of the cell's nuclear DNA. We present Monte Carlo simulations of the energy deposited by X-ray irradiation in mitochondria in cells with and without cytoplasmic GNPs. These simulations show that the presence of GNPs within the cytoplasm can significantly increase (3-4 fold) the number of ionisation clusters of both small and large sizes. As these clusters are strongly associated with DNA damage, these results suggest that mitochondrial DNA may be a significant target for GNP radiosensitisation when the nanoparticles cannot penetrate the cell nucleus.

1. Introduction

For more than a decade, Gold Nanoparticles (GNPs) have been the subject of extensive investigations as radiosensitising agents, following landmark work by Hainfeld *et al* [1]. By combining gold's high atomic number and perceived biocompatibility with the ability of sub-100 nm objects to penetrate the tumour vasculature, it was believed that GNPs acted effectively to increase dose to target structures. While there is now extensive evidence that GNPs radiosensitise cells, it is increasingly clear that their mechanism is not simply dose enhancement as originally believed. Experimental observations of GNP radiosensitisation have shown significantly greater effects than would be predicted from physical dose enhancement alone, suggesting that other processes drive radiosensitisation by GNPs [2].

In addition to the chemical and biological stresses which may be introduced by nanoparticles in a cellular system, there has also been interest in better understanding the physical distribution of dose on the sub-cellular scale. Early nanoscale models of GNPs demonstrated that interactions between radiation and GNPs led to dramatic dose heterogeneity on length scales of hundreds of nanometres, with localised doses of hundreds to thousands of Gray being deposited within volumes of tens to hundreds of nanometres in diameter. Analysis of these highly heterogeneous dose distributions through techniques developed for heavy ion therapy, such as the Local Effect Model (LEM), indicated that these dose heterogeneities drive significantly greater sensitisation than predicted from macroscopic dose enhancement alone, potentially explaining the increased radiosensitisation[3].

There remain significant questions about these early analyses, however, as they typically assumed uniform distribution of GNPs throughout a sensitive target volume, generally assumed to be the DNA contained within the cell nucleus. By contrast, in experimental systems many GNP preparations are seen

³ These authors contributed equally to this work



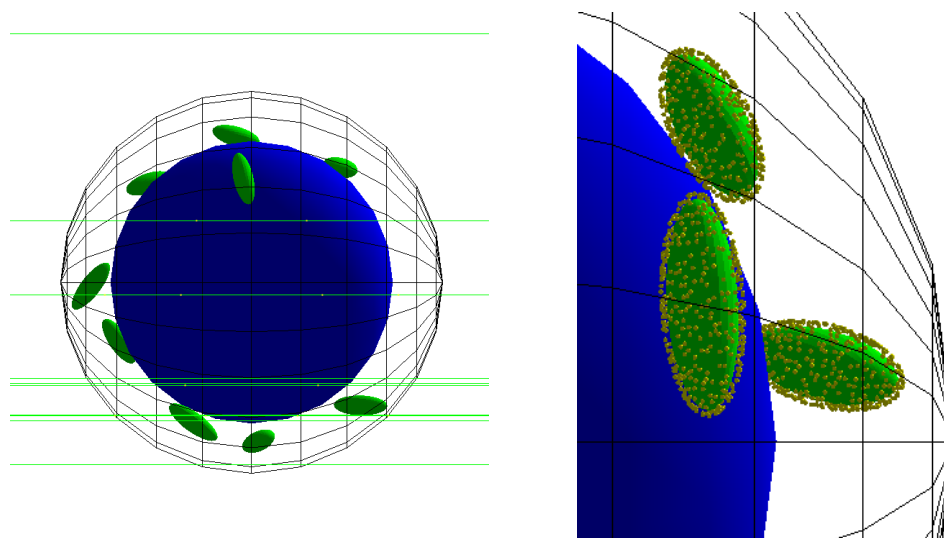


Figure 1. Left: Schematic illustration of modelled cell volume, showing outer cellular membrane, nucleus (blue) and smaller mitochondria (green). Right: Close-up of mitochondria, showing distribution of surface-bound GNPs (yellow).

to reside primarily or exclusively within the cytoplasm. In these cases, GNPs are necessarily tens to hundreds of nanometres away from any nuclear DNA, dramatically reducing the degree of dose heterogeneity seen by the DNA and the sensitisation predicted by models such as the LEM [4]. As significant sensitisation is seen in many such systems, this then raises the question of other cellular targets which may drive radiosensitivity.

One significant extra-nuclear target is the mitochondrion. These organelles are essential for cellular function (e.g. metabolism, apoptosis regulation, signalling, reactive species production). Mitochondria are the only extra-nuclear site to contain genetic material, but lack functional DNA repair [5], suggesting they may be sensitive to highly localised dose distributions in a similar fashion to the nucleus [6]. Importantly, as mitochondria are distributed throughout the cytoplasm and are small compared to the nucleus, mitochondrial DNA is much more likely to be close to a GNP and thus exposed to a high dose. Furthermore there is evidence that suggests GNPs may naturally accumulate on the surface of the mitochondria due to surface charge properties of the membrane [7]. To date, however, there have been few detailed studies of the dose and ionisation distributions within mitochondria when cells are irradiated in the presence of GNPs. In this work, we present an analysis of ionisation clustering effects in mitochondria with and without GNPs, to assess the potential significance of these effects in cellular radiosensitisation.

2. Methods

Radiation interactions with cells were calculated using the Geant4 Monte Carlo toolkit (version 10.1.p02) [8], including the Geant4-DNA package [9,10] to simulate ionisation on an event-by-event basis on the nanometre scale. A simple cellular model was implemented, consisting of an 11.5 μm diameter spherical cell, which contains an 8.5 μm diameter nucleus, and 30 elliptical mitochondria, with dimensions of 1.8 $\mu\text{m} \times 1 \mu\text{m} \times 0.6 \mu\text{m}$ along their axes, shown in Figure 1. These mitochondria were distributed randomly throughout the cytoplasm with random orientation. Exposure to 40 nm diameter GNPs was modelled, with 50 GNPs distributed at the surface of each mitochondrion.

Cells were exposed to monoenergetic X-rays of either 50 or 100 keV, with a total of 3.0×10^8 incident primary photons. The distribution of energy deposited within the mitochondria and nucleus was scored, together with the positions of ionisation and excitation events. To sample ionisation cluster sizes, virtual 'DNA segments' were placed within the irradiated volume. These were 10 nm by 5 nm cylinders, corresponding to approximately a 20 base pair segment of DNA. By scoring the density of ionisations

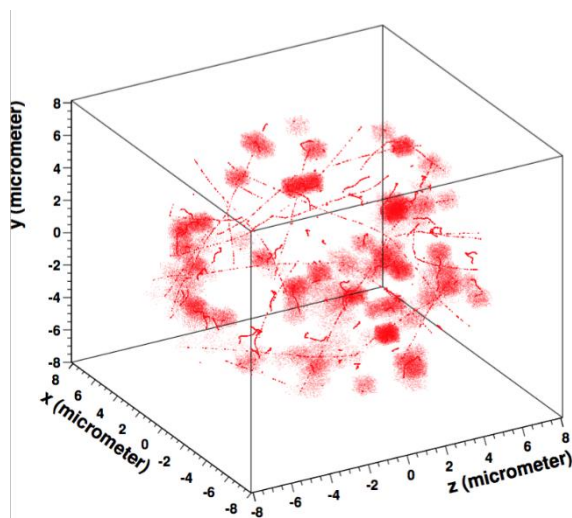


Figure 2. Map of secondary electron tracks for a simulated broad beam of 50 keV incident photons within the entire cell volume, 10^6 photons were modelled. Spontaneous clustering of ionisation events can be seen throughout the volume.

in these volumes, an estimate of the degree of ionisation clustering, and thus DNA damage, can be obtained [11].

3. Results

Figure 2 shows an illustration of the distribution of ionising events from a broad beam of 50 keV photons in the whole cell volume. Even in the absence of GNPs, stochastic clustering of ionisation events can be observed. Figure 3 shows the number of ionisation clusters of various sizes induced in mitochondria exposed to 50 or 100 keV X-rays, either with or without GNPs as described above. Although the total dose increase within the cell may be relatively small in these conditions, the number of ionising events increases substantially – by a factor of 3 or more. These effects are seen across all ionisation cluster sizes from 1 to 20 ionisation/excitation events per DNA segment, and for both 50 and 100 keV incident X-rays. By contrast, the impact on ionisation clustering for points within the nucleus is relatively small (a factor of 1.5 or less), indicating that DNA is subject to significantly more sensitisation in mitochondria rather than within the nuclear volume.

4. Conclusions

Cytoplasm-bound GNPs are not expected to lead to large increases in ionisation density within the nucleus, and thus are expected to lead to only modest sensitisation of nuclear DNA. However the small size of mitochondria, combined with their close proximity to cytoplasmic GNPs suggests that mitochondrial DNA will be subject to significant additional damage – with a several-fold increase in the number of ionisation clusters of all sizes in this simulation. If such clusters translate into DNA damage as is seen in the nucleus, then this may lead to a significant increase in mitochondrial damage and corresponding sensitisation of these organelles. Disruption of mitochondrial function can in turn have significant impact on the general functions of the cell. Mitochondria are essential for cellular metabolism, and disruption or dis-regulation of their function can lead to significant alterations in cellular energy transport, replication, and levels of oxidative stress within the cell. All of these effects may in turn impact on the cell's ability to survive exposure to ionising radiation, either by directly causing sufficient disruption of cellular function to lead to cell death or by combining with direct damage to nuclear DNA to prevent recovery following radiation exposure [6].

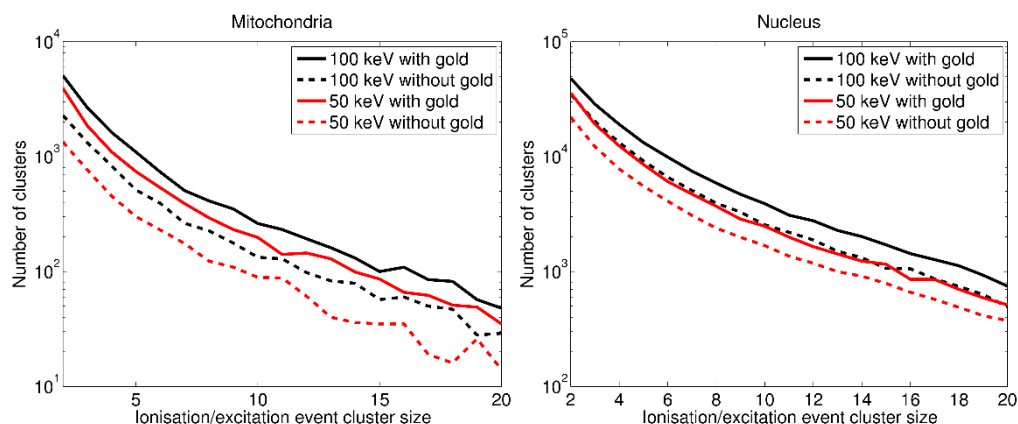


Figure 3. Impact of GNPs on ionisation clustering in mitochondria (left) and nuclei (right) for cells exposed to 50 keV (red) or 100 keV (black) X-rays. While ionisation rates increase in both regions, this is more pronounced in mitochondria (2.5-3 fold) than the nucleus (~1.5 fold).

These results indicate that, in cases where GNP are not internalised to the cell nucleus, mitochondria may be an important target for radiosensitisation through damage of mitochondrial DNA and disruption of the cellular metabolism. Further simulations to quantify the biological impacts of this ionisation clustering on mitochondrial DNA breakage, coupled with experimental investigations of disruption of mitochondrial function in the presence of GNPs, are needed to more accurately quantify the contribution of this pathway to GNP radiosensitisation.

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