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Radioactive gold nanoparticles: therapeutic impact in a prostate cancer model studied by electron microscopy and microdosimetry

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Several theoretical and experimental studies have confirmed the therapeutic potential of gold nanoparticles (Au NPs) as sensitizers for radiotherapy. In particular, the irradiation of Au NPs with low-energy photons such in low-dose rate brachytherapy (e.g. with the radioisotope 103Pd, ~ 20 keV photons; Figure 1.A), is particularly efficient for controlling the volume of prostate cancer tumors over months1. In fact, the probability of photons to interact with Au atoms through the photoelectric effect, is much higher at low photon energies and this has been considered until now as the driving mechanism for tumour control with Au NPs coupled to low dose rate brachytherapy. However, the secondary emissions produced by the photon-Au interaction (e.g. secondary electrons) are not very energetic and it is not clear at this step if their trajectory could reach the nucleuses and impact on the DNA. To improve our understanding of the radiosensitizing effect provided by Au NPs irradiated by low energy photons, microdosimetry studies are needed. In the present study, radioactive 103Pd:Pd:Au core-shell nanoparticles were synthesized according to a recently published methodology (Figure 1.B).2 The particles were injected in prostate tumours grown in the mouse model (PC3 cells injected in the flank of nude mice). The tumours were harvested at time points, sliced, and observed in transmission electron microscopy (TEM), thereby revealing biodistribution maps of Au NPs at the micrometric scale (Figure 1, C). A Monte Carlo-based dosimetric model was developed to evaluate at the sub-cellular scale (100 x 100 x 100 nm³ voxels) and based on the biological TEM images, energy deposition in the tissues containing 103Pd:Pd:Au NPs. The simulation results confirmed high-intensity dose deposition in the immediate vicinity of Au NPs, and not close to the nucleuses. This suggests that the strong tumour volume control observed experimentally in previous studies3, is most likely attributed to indirect damage (e.g. production of reactive oxygen species). Such mechanisms should be integrated in the model in the perspective of transferring Au NPs as radiosensitizers for low dose rate brachytherapy.

Figure 1. A) Conventional low dose-rate brachytherapy procedure for prostate cancer and B) new procedure involving injections of radioactive particles (103Pd:Pd-Au NPs). C) The intratumoral distribution of Au NPs was studied at the cell level with TEM (here: 24 h after injection). D) A microdosimetry study based these images and on a Monte-Carlo calculation approach, revealed energy deposition maps (Edep) at the cellular level (expressed in units of MeV/mCi).

References

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