Cellular Radiobiology

Iodine-125-labeled DNA-Triplex-forming oligonucleotides reveal increased cyto- and genotoxic effectiveness compared to Phosphorus-32 and external γ-irradiation

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Introduction: The efficacy of DNA-targeting radionuclide therapies might be strongly enhanced by employing short range particle emitter. To determine the gain of the biological impact per decay and radiation dose the biological effectiveness of the Auger electron emitter I-125 was investigated and compared to the ß⁻-emitter P-32 as well as to external homogeneous high dose rate γ-irradiation.

Methods: Triplex-forming oligonucleotides (TFO) bind to the DNA double helix in a sequence specific manner and are therefore a suitable carrier for Auger electron emitter to damage exclusively targeted DNA sequences [1]. Clonogenicity (colony-forming assay; CFA) and induction of DNA double strand breaks (DSB; 53BP1 foci assay) were investigated in SCL-II cells after exposure to I-125- or P-32-labeled TFO for different numbers of accumulated decays and were compared to external γ-irradiation (Cs-137; 0.7 Gy/min). The used TFO targeted a DNA sequence located in the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene. Point kernel calculations were employed for dosimetry on subcellular level.

Results: I-125-labeled TFO were shown to induce a pronounced decrease in cell survival and a marked increase of DSB with increasing numbers of accumulated decays per cell. Reduction in cell survival as measured in the CFA reached the D_{37} value at ~ 350 cumulated decays per cell, equivalent to ~ 1.2 Gy cell nucleus dose. P-32 labeled TFO displayed a weak cell killing ability and caused a small increase of 53BP1 foci up to ~ 4000 accumulated decays per cell, equivalent to ~ 1 Gy cell nucleus dose. The impact of P-32 was comparable to external γ-irradiation.

Conclusions: The reduction of cell survival and the increase of DNA damage proved to be much more pronounced in I-125-TFO exposed cells in comparison to P-32-labeled TFO per decay and per dose unit. This finding might be well explained by the high number of low energy Auger electrons emitted by I-125 per decay, leading to a high ionization density in the immediate vicinity of the decay site, probably producing highly complex DNA lesions, overcharging the cellular DNA-damage repair mechanism. The similar biological effectiveness of P-32-TFO exposure and external γ-irradiation proves the validity of the performed dose calculation on cellular level.

[1] Dahmen V, Kriehuber R. Int J Radiat Biol. 2012 Dec;88(12):972-9

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