Enhanced cyto- and genotoxic effects of Auger electron emitter-labeled DNA-Triplex-forming oligonucleotides in vitro

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Abstract: The efficacy of DNA-targeting radionuclide therapies might be strongly enhanced by employing short range particleemitter. However, the therapeutic use of radionuclides requests a thorough radiation dosimetry especially when short-range particles are released. In this study we compared the ß-emitter P-32 and the Auger electron emitter I-125 in terms of biological effectiveness per decay and per unit dose when located in the close proximity to the DNA by using Triplex-forming oligonucleotides (TFO). TFO bind to the DNA double helix in a sequence specific manner. Therefore, TFO seem to be a suitable carrier for radionuclides emitting short-range electrons to damage exclusively targeted DNA sequences. We investigated clonogenicity (colony-forming assay; CFA) in the human squamous carcinoma cell line II (SCL-II) and the induction of DNA double strand breaks (DSB; 53BP1 foci assay) after exposure with P-32 or I-125 labeled TFO for different numbers of accumulated decays. The employed TFO targeted a specific DNA sequence located in the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene.

Results: I-125-labeled TFO binding to single targets were shown to induce a pronounced decrease in cell survival and an increase of DSB with increasing numbers of accumulated decays per cell. The reduction in cell survival as measured in the CFA reached the D37 value at ~ 350 accumulated decays per cell, equivalent to ~ 1.2 Gy cell nucleus dose. Using the same TFO but labeled with P-32 revealed neither a significant decrease of the survival fraction nor an increase of the DSB rate in SCL-II cells up to ~ 4,000 accumulated decays per cell which is equivalent to ~ 1 Gy cell nucleus dose.

Summary & Conclusions: The reduction of cell survival and the increase of DNA damage proved to be much more pronounced in I-125-TFO transfected cells than observed after exposure with the P-32-labeled TFO per decay and per dose unit. This can be 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 very complex DNA lesions, overcharging the cellular DNA-repair mechanisms.

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